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THEME ISSUE
Emergency [illegible] Management of Cardiovascular Emergencies

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THEME ISSUE

Emergency Department Management of Cardiovascular Emergencies

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Introduction

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Cardiovascular Emergencies

WE HAVE SEEN IMPRESSIVE ADVANCES in the field of heart disease in recent years. In terms of prevention, we now have a much clearer picture of the pathogenesis and growth of atherosclerotic plaques. And a host of predisposing genetic and environmental factors have been identified. These include not only the well-known risk factors—diabetes, hypertension, smoking, stress, sedentary lifestyle and the disorders of lipid metabolism—but also elevated levels of lipoprotein (a), homocysteine and C-reactive protein.

The vulnerable plaque is now a focus of many investigators. These soft plaques appear to be smoldering, volcano-like excrescences that can rupture and release thromboplastic mediators that lead to clot formation and that may occlude the vessel lumen. Our new knowledge has led to the extensive and successful use of antiplatelet as well as anticoagulant therapies for the patient with an acute cardiac ischemic syndrome. It has also led to new theories about the role of inflammation and perhaps occult infection in the process of plaque softening and rupture.

Recent studies have consistently favored the use of angioplasty over thrombolysis for acute myocardial infarction. This is consistent with prior findings of the lack of evidence for a role for thrombolysis in non-ST elevation infarction and other ischemic variants. Consequently, there is now a strong tendency to provide the services of the catheterization laboratory for these patients. As this process has evolved, some hospitals without cardiac surgical programs have had to offer invasive cardiologic services for the patient with acute ischemic cardiac disease. Several trials have shown that these services can be safely provided at these sites as long as they have a coordinating center that offers emergency cardiac surgery as a backup.

Although the last update to the emergency care guidelines for basic life support (BLS) and advanced cardiac life support (ACLS) was issued in 2000, many providers are still struggling to interpret and implement the new material. The new ACLS medications that were added are arginine vasopressin and amiodarone. And vasopressin either replaces or is used with epinephrine for cardiac arrest. Amiodarone is used for unconvertible and recurrent ventricular fibrillation and for treating ventricular tachycardia, for which it supersedes procaine amide.

For the first time, the BCLS guidelines include the bystander application of closed chest compression without ventilation. Some evidence shows that during the early phase of resuscitation, ventilation is not entirely necessary. It has also been shown that early chest compression cardiopulmonary resuscitation (CPR) is vastly better than delayed perfusion. (This guideline was also a response to the understandable but unfortunate reluctance of both professional and lay rescuers to perform mouth-to-mouth ventilation.)

Recently we have participated in the patient access defibrillation (PAD) trials, in which residents of large apartment complexes and people in other institutions received CPR training with or without an automated external defibrillator program (AED). Patient survival was the dependent variable. Unfortunately, there was only a small increase in survival in the studied populations. So the presence of an AED in these settings was not effective as a public health measure. But the demographics of these patients help explain the lack of efficacy; in our study, the victims of sudden death in the community were mainly the elderly living alone.

There has also been a great deal of progress in our understanding and treatment of the patient with heart failure. We now have a more complete understanding of the remodeling process that the heart undergoes prior to and during heart failure. It is clear that many of the homeostatic mechanisms affecting the cardiovascular system are in themselves ultimately destructive to normal functioning. The remodeling of the heart's fabric has a major impact on electrical-mechanical coordination of contraction. The hypertrophy and fibrosis that is associated with remodeling also decreases the compliance of the heart. The decreased compliance in turn interferes with left ventricular diastolic filling and, in the case of hypertrophic cardiomyopathy, can also obstruct left ventricular ejection.

Neurohormonal responses of the heart in failure are both homeostatic and pathophysiologic factors presenting major new foci for management. The first medication that seems to counter the vasoconstriction and salt and water retention associated with chronic and acute heart failure is brain natriuretic peptide, a natural vasodilator and diuretic. Whether this parenterally administered agent has a long-term effect in management still remains to be determined. But it is clear that the issue of unloading the heart is a key management strategy that can be fulfilled pharmacologically.

The use of elective left ventricular pacing to "resynchronize" the heart is another recent treatment modality for managing congestive heart failure (CHF). Initially, this procedure was used for hypertrophic cardiomyopathies, but it has been found that many patients with cardiac hypertophy have abnormal excitation pathways that reduce the efficacy of ejection. Some but not all of these patients have a widened QRS pattern or frank bundle branch blocks. A number of studies have now shown that resynchronization therapy can increase the ejection fraction and cardiac indices of many patients with severely depressed cardiac function.

While death from acute myocardial infarction has been reduced to approximately 8% of hospitalized patients, the incidence of sudden death in the community has not changed significantly. Some of these deaths are due to intracranial hemorrhage, pulmonary embolism and cardiomyopathies, but the vast majority are caused by dysrhythmic events due to ischemic heart disease. However, the use of antidysrhythmic medications has diminished because a majority of these drugs, while decreasing ectopic rhythms, have not led to improved outcomes and may be proarrhythmic. Amiodarone is the only notable exception to this statement, as its use has accelerated for both atrial and ventricular rhythm disturbances. Radio wave ablation and the use of implantable defibrillators have replaced antidysrhythmic medications, with significantly better outcomes.

Because of the rapid growth of our knowledge base and therapeutic capabilities, this is an exciting time in the field of emergency cardiac care. The emergency department is one of the clinical hubs where these advances are made available to patients. These patients may be critically ill on arrival or at risk to deteriorate and become unstable if proactive interventions are not instituted. Emergency physicians must be trained and able to provide emergency cardiac care to this diverse patient population, which includes individuals with acute myocardial infarction and the more common presentation of acute coronary syndrome. Physicians must be prepared to treat patients with acute or chronic heart failure and a host of acute and chronic rhythm disturbances. They must know how to help patients with problems related to implanted devices. They may also need to assess patients with valvular heart disease presenting with both preoperative and postoperative problems. They will be seeing more patients with heart transplants, who will be presenting with problems related both to graft rejection and intrinsic recurrent vascular disease in the transplanted heart.

As emergency physicians, we can best help and support these acutely ill and complex patients by maintaining our cardiac knowledge base at a very high level and by working closely with our colleagues, the cardiologists and cardiothoracic surgeons. It is our intention that this issue of the *Journal* will present a critical update of those recent advances in cardiology that have been introduced into emergency departments. These are some of the advances about which we will need an in-depth understanding in order to evaluate and treat our patients and communicate effectively with our colleagues.

Atherothrombosis in Acute Coronary Syndromes:

Mechanisms, Markers, and Mediators of Vulnerability

ERIC J. WASSERMAN, M.D., AND NEAL M. SHIPLEY, M.D.

Abstract

We review the concept of atherothrombosis and the critically important role of inflammation in the development of acute coronary syndromes (ACS). Inflammation is now known to be a major driving force underlying the initiation of coronary plaques, their unstable progression, and eventual disruption, and it also contributes significantly to thrombotic complications that occur in ACS. In addition, we discuss the various local mediators and systemic markers that are involved in the inflammatory process, and review the concepts of "vulnerable plaque," "vulnerable blood," "vulnerable myocardium," and the "vulnerable patient" who is at increased risk for ACS.

Key Words: Inflammation, markers, mediators, vulnerable, acute coronary syndrome.

Introduction

ATHEROTHROMBOSIS is essentially defined as atherosclerosis and its thrombotic complications. With respect to coronary artery disease (CAD), the term implies that there is an interdependent relationship between plaque growth and arterial thrombosis that provides the framework for precipitating an acute coronary syndrome (ACS) (1). Inflammation plays a central role throughout the entire disease progression (2), serving as the engine that runs the atherothrombotic machine. Plaques within the coronary circulation become "high-risk," "unstable" or "disruption-prone" ("vulnerable plaque") in response to a wide array of local and systemic influences that are patient-specific. Thrombus formation in association with these lesions may be accelerated or amplified under these same influences ("vulnerable blood") (3). Similarly, at-risk myocardium that is prone to rhythm disturbances or subject to ischemic flows is likely to experience dysfunction ("vulnerable myocardium") (4). Thus, it is not simply that (given ample time) a largely occlusive lesion invariably ruptures and thromboses a coronary vessel. Rather, a combination of risk factors contributes to a vulnerable plaque composition, prothrombotic milieu, and susceptible heart—conditions that strongly favor the clinical manifestation of unstable angina, myocardial infarction, or sudden cardiac death. In order to better predict who is at risk for an acute coronary event ("vulnerable patient") (4), knowledge of the local and systemic contributors to plaque initiation, progression, disruption, and thrombotic complication is fundamental.

Atherogenesis, Remodeling, and Plaque Disruption

Advances in the understanding of atheromatous coronary disease have focused our attention on the composition of the plaque rather than the degree of stenosis as the major pathophysiologic determinant of disease. Nonstenotic lesions are far more frequent than stenotic plaques, and it has been observed that in up to two-thirds of patients with ACS, relatively small, nonocclusive lesions within a coronary artery may become complicated by thrombus and rapidly progress to total occlu-

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Glossary

ACS = acute coronary syndrome
ADP = adenosine diphosphate
Apo(a) = apolipoprotein(a)
AT_1 = type 1-angiotensin
CAD = coronary artery disease
CAM = cell adhesion molecule
CD40L = CD40 ligand
CRP = C-reactive protein
EC = endothelial cell
ECM = extracellular matrix
HDL = high-density lipoprotein cholesterol
IVUS = intravascular ultrasound
LDL = low-density lipoprotein cholesterol
Lp(a) = lipoprotein(a)
MMP = matrix metalloproteinase
PAI-1 = plasminogen-activator inhibitor type-1
PPAR = peroxisome proliferator-activated receptors
sCD40L = soluble, biologically active CD40L
SMC = smooth muscle cell
TF = tissue factor
TFPI = TF pathway inhibitor
TIMP = tissue inhibitors of metalloproteinases
TNF = tumor necrosis factor

sion (5). In contrast to plaques that form in vascular beds of the brain and periphery, syndrome-producing "culprit" lesions of the coronary arteries do not necessarily create critical degrees of luminal stenosis as they develop. Thus, what should be considered a high-risk lesion may not be apparent with coronary angiography despite the fact that the patient may be at increased risk of experiencing an acute adverse event (6). Identification of individuals who have—or who are likely to generate—vulnerable or unstable plaque phenotypes, in addition to those with pre-existing subocclusive or occlusive disease, represents a shift from traditional strategies of coronary imaging and risk stratification.

The atherosclerotic process occurs within the intima of large- and medium-sized arteries throughout the body and is present as early as the first few years of life (7). Under the influence of a host of behavioral, biochemical, environmental, and genetic factors, plaques (in susceptible individuals) generally progress through various phases of evolution, from stable, asymptomatic, grossly invisible lesions to unstable, high-risk atheromas. The earliest changes begin within the endothelium, where activated endothelial cells (ECs) recruit monocytes and T lymphocytes to the vessel wall (7). Endothelial dysfunction drives this process, which is marked by EC expression of leukocyte and vascular-cell adhesion molecules (CAMs) and increased endothelial permeability to lipoproteins, leukocytes, and other inflammatory mediators (8). Increasing numbers of atherogenic lipoproteins and T lymphocytes within the intima stimulate monocytes to become macrophages and then macrophage-derived, lipid-laden foam cells as they ingest modified lipoproteins. Smooth muscle cells (SMCs) migrate and proliferate, leukocyte recruitment amplifies, and platelet aggregates adhere to injured endothelium in response to a variety of inflammatory mediators secreted by ECs, activated leukocytes, SMCs, and platelets (9). These lesions represent what are commonly referred to as "fatty streaks" and are often present in individuals by early adulthood. With continued progression, these plaques accumulate pools of extracellular lipid deposits that surround increasing numbers of inflammatory cells, SMCs, and connective tissue elements, all of which comprise a pro-atherogenic, prothrombotic, dynamic environment known as the "extracellular matrix" (ECM) (10). In response to a variety of cytokines and growth factors (e.g., transforming growth factor-β [TGF- β]), a fibrous cap, composed primarily of SMCs and collagen, develops around the expanding lipid core, walling it off from the lumen (11). The atheromatous core accumulates larger, more confluent amounts of extracellular lipids along with inflammatory mediators (e.g., interferon-γ) and proteolytic enzymes (e.g., matrix metalloproteinases [MMPs]) that contribute to thinning of the now well-established fibrous cap, by digesting its components (12).

Plaque disruption during this phase often results in the formation of mural thrombus, but may quickly progress to total occlusion in the setting of increased blood thrombogenicity (13). Through a continuous process of ECM remodeling, more advanced, complicated lesions develop. These plaques, which often, but do not always, create significant degrees of luminal stenosis, are characterized by a degraded fibrous cap with superimposed organizing thrombus and a well-formed, mostly acellular necrotic core containing oxygen radicals, oxidized lipids, dying foam cells, erythrocyte membranes and apoptotic cellular debris ("thin-cap fibroatheroma"). Given the appropriate stimuli, these high-risk atheromas may progress to largely occlusive and calcified or fibrotic atheromas, which may in turn trigger signs and symptoms of angina pectoris and ACS that occur secondary to acute thrombosis or during periods of inadequate collateral/luminal blood flow.

The progression of a fatty streak to a high-risk atheroma occurs through a continuous process of ECM remodeling. Dysregulation of ECM metabolism may result in an accelerated accumulation of lipids and foam cells (14), a net increase in collagen resorption with subsequent weakening of the fibrous cap (15), and compensatory changes in vessel wall architecture leading to ectasia (16). Neovascularization in atherosclerotic arteries introduces fragile intimal microvessels (vasa vasorum), which may rupture into the core, resulting in repeated, often subclinical, intraplaque hemorrhage (17). As these clots reorganize and are layered with fibrous tissue, the lesion advances (18). Expansive remodeling of the ECM results in outward growth of the plaque, increasing the circumference of the diseased section of artery and preserving the lumen (19). As the extent of luminal narrowing is inversely proportional to the degree of expansive remodeling (20), relatively nonstenotic segments observed during angiography may harbor advanced, disruption-prone plaques (21) that have been identified as culprit lesions in patients with ACS, using intravascular ultrasound (IVUS) (19). In contrast, constrictive remodeling of plaques, which promotes luminal stenosis, is more commonly associated with stable plaque phenotypes that are evident in patients with stable angina pectoris (22).

Early studies described frank rupture of a plaque as the cause of thrombosis in nearly three-quarters of subjects with sudden cardiac death (23). More recent observations suggest that roughly 60–70% of acute coronary thromboses result from plaque rupture, while as many as 30–40% are associated with superficial erosion of the high-risk plaque (24). Necropsy studies of atheromatous coronary arteries reveal some plaque disruptions to be clinically silent (25). Repetitive cycles of subclinical rupture and healing appear to be a potent stimulus for growth and often result in an accelerated progression toward advanced disease (26).

Thrombosis

Disruption of an atherosclerotic plaque, via rupture or erosion with *in situ* formation of a blood clot that occludes the lumen of a coronary artery, is the pivotal event in the atherothrombotic process leading to ACS. Inflammation plays a key role during thrombogenesis as well, as procoagulant factors within the ECM are exposed to luminal blood flow at sites where plaque disruption has occurred (27). Stimulated by inflammatory mediators, circulating platelets adhere to damaged endothelium and form aggregates that become enmeshed with fibrin (3). Given the appropriate mixture of disturbed blood flow, inflammation, and thrombogenic potential, occlusive thrombi may trigger ACS even in the absence of visible plaque disruption (28). A growing body of evidence suggests that hyperlipoproteinemia, hypertension, diabetes, hyperhomocysteinemia, cigarette smoking, apoptosis, and the presence of tissue factor (TF), among other conditions, augment the inflammatory and hemodynamic response to vascular injury and feed the coagulation cascade resulting in accelerated thrombogenesis.

Hyperlipidemia

Excess cholesterol deposition within the intimal layer of the vascular wall is a central process in the progression toward unstable atherothrombotic disease (29). Intramural accumulations of extracellular lipids have been observed consistently in a majority of culprit lesions from ACS patients (30). High plasma levels of low-density lipoprotein cholesterol (LDL) and triglycerides (31), and low plasma levels of high-density lipoprotein cholesterol (HDL) have been implicated as major independent cardiovascular risk factors in countless studies, and LDL-lowering is associated with an up to 30% reduction in the incidence of acute coronary events in clinical trials assessing statin pharmacotherapy (32). It has been argued that these lower-density lipoproteins exert pro-atherogenic and prothrombotic influences that contribute to plaque progression, instability, and accelerated thrombogenesis through a variety of interrelated mechanisms.

Structurally and functionally similar to LDL, lipoprotein(a) [Lp(a)] has been implicated by a growing body of research as a “key player” in atherothrombogenesis (33). A major component of Lp(a), apolipoprotein(a) [Apo(a)] is structurally similar to plasminogen and competes with plasminogen by inhibiting its binding to fibrin. Larger amounts of Lp(a) are detected in the lesions of ACS patients when compared with those of stable angina patients, and extensive macrophage colocalization with Lp(a) is observed within culprit lesions, evidence supporting the hypothesized role of Lp(a) as a contributor to both inflammation and plaque disruption (34). Convincing data also suggests that Lp(a) is thrombogenic and promotes coagulation (35), inhibiting fibrinolysis through its interaction with fibrin (36). Altogether, these studies support a major atherothrombotic function of Lp(a) in the progression toward ACS, yet clinical trials with lipid-lowering agents that specifically target Lp(a) are lacking (37).

Hypertension

The recent literature pertaining to hypertension and atherosclerosis has focused on angiotensin II, a potent vasoconstrictor and principal product of the renin-angiotensin system. Aside from elevating blood pressure, angiotensin II contributes to atherogenesis by inducing endothelial dysfunction (38), stimulating SMC growth (39), attracting monocytes (40), and enhancing macrophage uptake of oxidized lipoproteins (41).

Recent work examining the structure of G protein-coupled type 1-angiotensin (AT_1) receptors suggests that covalent dimerization of AT_1 receptors on the surface of monocytes may account for the pro-inflammatory and atherogenic changes seen in hypertensive patients (42). These observations provide the impetus for the development of monocyte-selective therapeutic agents that specifically target G protein-coupled receptor function in an effort to minimize the atherogenic contribution of hypertension to plaque initiation, progression and acute complication (43).

Diabetes

Diabetes also has a multifactorial role in promoting atherothrombosis. Improved glycemic control has been demonstrated to be associated with a reduction in the risk of cardiovascular disease (44). Hyperinsulinemia alone has been investigated as an independent risk factor, one that increases susceptibility to thrombosis by causing elevated levels of plasminogen-activator inhibitor type-1 (PAI-1) (45, 46). Increased blood thrombogenicity has been demonstrated in diabetics, as has increased platelet reactivity and aggregability (47). The thiazolidinediones have been demonstrated to lower PAI-1 levels, and the improved glycemic control seen with these agents may lead to an overall reduction in atherothrombotic events (48).

Smoking

Cigarette smoking is a well-established risk factor for atherosclerosis and premature CAD. Decades of research have identified several mechanisms that are likely to contribute to accelerated atherothrombogenesis in patients with ACS who smoke. These mainly include EC dysfunction (49), increased oxidative stress (50) and increased blood thrombogenicity (51), factors that may work alone or in concert with one another to generate a pro-atherogenic, prothrombotic environment conducive to the development of high-risk atherosclerotic disease. Cigarette smoking produces oxygen-derived free radicals and lipid peroxides that impair the endothelium and promote LDL oxidation (52), monocyte adhesion (53), and platelet aggregation. Smoking markedly attenuates endothelium-dependent vasodilatation (54), which suggests that smoking may play a crucial role in the transformation from stable to unstable coronary disease. Additionally, impaired thrombolytic activity is found in smokers (55). These factors are likely to account for the hypercoagulable state and reduced fibrinolytic potential that have been observed in chronic smokers both with and without CAD (56).

Other Agents Implicated in Atherothrombosis

Tissue factor and apoptosis. A glycoprotein abundantly expressed on the surface of a variety of different cell types within atherosclerotic plaques, TF initiates the external clotting cascade and may be a major contributor to increased blood thrombogenicity and accelerated thrombogenesis in ACS patients (57). An animal study reported that monoclonal antibodies directed against TF can decrease thrombogenicity and inhibit both thrombus formation and re-occlusion in diseased arteries (58). Endogenous tissue factor pathway inhibitor (TFPI) appears to be an efficient inhibitor of TF activity, and a reduction in local plaque thrombogenicity has been observed in disrupted human plaques through inhibition of the TF pathway by exogenous TFPI (59).

The contribution of TF to increased blood thrombogenicity seems to be closely linked to apoptosis, or programmed cell death (60), a process that occurs in virtually all cell types present within the fibrous cap and necrotic core of atherosclerotic lesions (61). It has been proposed that apoptotic cells and debris, rich in phosphatidylserine, provide a potent thrombogenic stimulus to a disrupted plaque by activating TF (62). It has also been observed that apoptosis of SMCs occurs to a greater extent within the atherosclerotic plaques of ACS patients as compared with those of stable angina patients (63). Taken all together, these findings highlight an important procoagulable, pro-inflammatory contribution of both TF and apoptosis to overall vulnerability in CAD, and the development of therapeutic agents that inhibit the TF pathway at various steps is currently underway.

Homocysteine. More than three decades of research have implicated elevated plasma homocysteine as an independent risk factor for atherosclerotic disease (64). Studies of patients with inborn errors of homocysteine metabolism have identified accelerated CAD that often resulted in a first myocardial infarction by the second decade of life (65). In patients without genetic defects who have elevated plasma homocysteine, the relative risk of CAD was found to be 24 times that of controls (66). Furthermore, a threefold increase in the risk of acute myocardial infarction was reported in a prospective evaluation of men with homocysteine levels just 12% above normal, after accounting for traditional CAD risk factors (67).

Evidence suggests that homocysteine is prothrombotic (68), damages vascular endothelium (69), interferes with endothelium-dependent vasodilation (70), attenuates the effects of NO (71), and increases platelet adhesion (72) and oxidative stress (73). Moreover, a recent study reported an increase in collagen synthesis by vascular SMCs cultured with homocysteine (74), findings which support a pro-atherogenic role of homocysteine.

C-reactive protein. C-reactive protein (CRP), a nonspecific but highly sensitive plasma marker of systemic inflammation, has recently been proposed as an independent risk factor for cardiovascular disease (75, 76). However, it remains unclear whether CRP directly influences plaque initiation and progression (77) or simply represents the inflammatory contribution of another factor.

Plasma elevations of CRP have been reported in patients with acute ischemia and myocardial infarction, and are predictive of the risk of recurrent ischemia among hospitalized patients with unstable angina (78). Recent research suggests that CRP activates ECs and monocytes, and that pharmacologic agents can modulate its effects (79). CRP levels were directly related to the risk of a first myocardial infarction in apparently healthy men given aspirin (80), further evidence supporting a role for anti-inflammatory therapy in ACS prevention. Periodic monitoring of CRP in addition to LDL in patients receiving statin therapy is supported by recent data showing improved clinical outcomes in those with low post-treatment CRP (<2 mg/L) as compared to those with higher levels, regardless of the resultant LDL cholesterol level (81). Future research will hopefully shed more light on the significance of CRP and other inflammatory mediators in the progression toward unstable CAD.

PPARs. Functioning as ligand-receptor transcription factors, peroxisome proliferator-activated receptors (PPAR) belong to a superfamily of nuclear receptors that are involved in gene expression throughout the body (82). At the cellular level, these PPAR target genes control a variety of biological processes, including glucose homeostasis, lipid metabolism and inflammation (83), and studies have attempted to establish a link between PPAR signaling and atherothrombotic disease (84, 85). Three subfamilies of PPARs exist: PPAR-α, PPAR-β/δ, and PPAR-γ. PPAR-γ has been the most extensively studied; it has been implicated in the regulatory phase of fatty acid storage within adipose tissue, and is highly expressed by foam cells, SMCs, ECs, mononuclear cells, and macrophages within atherosclerotic plaques (86). Activation of PPAR-γ within the arterial wall has been shown in animal models to lead to a regression of atherosclerotic disease. PPAR-γ activation is likely to result in enhanced fibrinolysis and decreased blood thrombogenicity through its negative effects on PAI-1 and fibrinogen concentrations (87). Finally, PPAR-γ activators have been reported to inhibit the expression of inflammatory mediators including MMPs, CAMs, and cytokines, and may lead to a reduction in plaque inflammation or disruption through one or more of these pathways (88). Notably, fibrate therapy for hyperlipidemia and thiazolidinedione therapy for type 2 diabetes utilize the PPAR-α and PPAR-γ pathways to achieve their respective clinical effects.

Matrix metalloproteinases. MMPs are a diverse family of powerful, zinc-containing enzymes expressed by macrophage-derived foam cells, SMCs and other vascular cells within atherosclerotic lesions (89). It has been previously demonstrated that MMPs are responsible for remodeling of the ECM during all stages of atheromatous development and may directly contribute to fibrous cap weakening and plaque rupture within diseased arteries (90). Together with MMPs, endogenous inhibitors of MMPs—termed "tissue inhibitors of metalloproteinases" (TIMPs)—are expressed within plaques and are capable of inhibiting the matrix-degrading potential of MMPs, presumably by interfering with the cleavage of the zymogen to its active form (91). Current research has focused on MMP inhibition as a potential therapeutic strategy (92), although pharmacologic agents that target specific MMP proenzymes or enhance TIMP activity *in vivo* have yet to be developed (93). Moreover, recent investigations suggest that at least some MMPs are beneficial, participating in the healing of wounds and strengthening of tissues (94, 95). A greater understanding of the pleiotropic effects of MMPs in human atheromas is needed if we are to determine whether therapy aimed at these proteins lessens the risk of unstable CAD.

Key Concepts

1. Atherothrombosis is defined as atherosclerosis and its thrombotic complications.
2. Acute coronary syndromes encompass unstable angina, myocardial infarction, and sudden cardiac death, entities that represent clinical endpoints of the atherothrombotic process.
3. Identification of the vulnerable patient requires careful assessment of plaque vulnerability, blood vulnerability, and myocardial vulnerability in order to more accurately determine an individual's risk of ACS.
4. A growing body of evidence suggests that conditions such as hyperlipoproteinemia, hypertension, diabetes, hyperhomocysteinemia, cigarette smoking, apoptosis, and the presence of TF, among others, augment the inflammatory and hemodynamic response to vascular injury and feed the coagulation cascade resulting in accelerated thrombogenesis.
5. CRP, MMPs, CD40L, and PPARs appear to be intimately involved in plaque progression and may represent therapeutic targets and/or markers of vulnerability within the arena of ACS prevention and treatment.

CD40 ligand. CD40 ligand (CD40L) is an immunoregulatory transmembrane protein that belongs to the tumor necrosis factor (TNF) super family. It is expressed on the surfaces of many cell types, including leukocytes, ECs, SMCs, macrophages, and activated platelets (96). Ligand-receptor binding on these cells triggers the expression and secretion of a variety of pro-inflammatory and procoagulant mediators, including CAMs, cytokines, chemokines, growth factors, MMPs, and TF (96). Recent data suggest that CD40L plays a central role in the inflammatory process that contributes to plaque destabilization in CAD (97), and elevations in soluble, biologically active CD40L (sCD40L) have been demonstrated in the serum of ACS patients (98). Notably, inhibition of both platelet activation and sCD40L release is possible through interference with adenosine diphosphate (ADP)-receptor binding and through GPIIb/IIIa receptor inhibition (99, 100), processes which may exert an overall negative influence on platelet aggregation. This expanding body of evidence lends support to the hypothesis that pharmacologic antagonism of CD40L may help ameliorate the thromboinflammatory cascade of events that contributes to plaque progression and thrombosis in patients with ACS (101). However, it remains unclear whether CD40L has a primarily pathogenetic role or is simply a marker of local or systemic inflammation.

Conclusions

In summary, the atherothrombotic process culminating in ACS is both multifactorial and patient-specific. Inflammation appears to play a critical role throughout this process. The concept of the vulnerable patient takes into account contributions made by plaque morphology and composition, blood thrombogenicity and myocardial susceptibility, when determining an individual's risk of an acute coronary event. Traditional cardiac risk factors that predispose an individual to atheromatous disease are only part of the equation and must be considered within the setting of other local and systemic contributors that may adversely affect coronary plaque progression and thrombotic complication. Our advances in the understanding of the atherothrombotic process will hopefully lead to an earlier detection of vulnerable plaques, a greater predictive value of serum markers, and more specifically targeted pharmacological interventions to find and treat the vulnerable patient at risk of ACS.

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New Approaches to Out-of-Hospital Cardiac Arrest

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Abstract

Out-of-hospital cardiac arrest (OOH-CA) is a leading cause of mortality and the focus of significant research. Recent studies provide new evidence that may change our management of OOH-CA and improve outcomes.

The findings of two recently published studies of OOH-CA are reviewed in this article. The first, the Public Access Defibrillation Trial, was a randomized, controlled trial of public access defibrillation in 993 community facilities in the U.S. and Canada. It demonstrated that a community strategy to train laypersons to respond to cardiac arrests significantly increased survival to hospital discharge following OOH-CA in nonresidential community units with community members trained and equipped to provide public access defibrillation, compared to community units with community members trained to provide cardiopulmonary resuscitation (CPR) without any capacity for defibrillation. The second, the European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study, was a randomized, controlled, double-blinded trial that compared vasopressin to epinephrine as the initial pharmacological therapy for 1,219 patients who sustained OOH-CA. The study demonstrated that vasopressin is similar to epinephrine for OOH-CA due to ventricular fibrillation or pulseless electrical activity, and superior to epinephrine for the initial treatment of asystolic arrest; it also demonstrated that the combination of vasopressin and epinephrine is superior to epinephrine alone in the treatment of refractory, out-of-hospital cardiac arrest. Studies on alternative CPR techniques and adjunctive devices for CPR were also reviewed.

We conclude that pre-hospital access to defibrillators and the use of vasopressin in the management of asystole hold promise for improving survival for patients with out-of-hospital cardiac arrest.

Key Words: Cardiac arrest, out-of-hospital cardiac arrest, defibrillation, public access defibrillation, cardiopulmonary resuscitation, alternative cardiopulmonary resuscitation, interposed abdominal compression cardiopulmonary resuscitation, active compression-decompression cardiopulmonary resuscitation.

Introduction

Despite marked improvements in pre-hospital emergency care over the past three decades and declines in overall mortality from cardiovascular disease, out-of-hospital cardiac arrest (OOH-CA) continues to have a mortality rate ranging from 85–97% (1, 2). Decreasing the mortality from OOH-CA is the active focus of resuscitation research. We review two recently published articles suggesting that new approaches to the management of OOH-CA may improve outcomes.

Public Access Defibrillation

Early cardiopulmonary resuscitation (CPR) and timely advanced life support are known to improve survival from OOH-CA; mortality is most directly related to the interval between collapse and defibrillation (3, 4). Ventricular fibrillation (V-fib) is the most commonly encountered cardiac arrest rhythm. Since the introduction of electrical shock therapy, trained pre-hospital personnel have used portable defibrillators on victims of out-of-hospital cardiac arrest. Historically, efforts to improve survival from OOH-CA largely focused on decreasing emergency medical services (EMS) response time, in part by increasing the number of trained responders who can provide defibrillation. More recently, technological advances have created automated external defibrillators (AEDs), which do not require the operator to have knowledge of electrocardiography (5–8). Basic emergency medicine technicians (EMTs), firefighters and police officers have, in many communities, been trained to use AEDs on victims of OOH-CA (9–12).

There are constraints inherent in delivering a trained responder to a victim of cardiac arrest outside of the hospital. These constraints include traffic congestion, high-rise buildings in urban areas, and lengthy transit times in rural areas. This problem inspired a movement to place AEDs in the community for use by laypersons; the program is called "public access defibrillation" (PAD). Early reports of successful PAD programs in airports, casinos and health clubs and on airlines were widely publicized by community leaders and the AED industry (8, 13–17), but left many unanswered questions about the efficacy, implementation, and long-term management of PAD programs in the community (4–7, 10–12, 18–21).

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Glossary

ACD-CPR: active compression-decompression CPR
ACLS: advanced cardiac life support
AED: automated external defibrillator
AHA: American Heart Association
BLS: basic life support
CPR: cardiopulmonary resuscitation
ECC: emergency cardiac care
ED: emergency department
EMS: emergency medical services
EMT: emergency medical technician
IAC-CPR: interposed abdominal compression/CPR
ITV: impedance threshold valve
MIDCM: minimally invasive direct cardiac massage
OOH-CA: out-of-hospital cardiac arrest
PAD: public access defibrillation
PEA: pulseless electrical activity
PTACD: phased thoracic-abdominal compression-decompression CPR
ROSC: return of spontaneous circulation
V-fib: ventricular fibrillation

The PAD Trial, funded by the National Heart, Lung and Blood Institute and the American Heart Association (AHA), was a randomized, controlled trial designed to test the hypothesis that PAD significantly increases survival in OOH-CA by reducing the time interval from collapse to defibrillation (22). The primary outcome was survival to hospital discharge following OOH-CA in community units with community members trained and equipped to provide public access defibrillation, compared to community units with community members trained to provide CPR without any capacity for defibrillation. Twenty-four participating research sites in the United States and Canada enrolled 993 community units (e.g., high-rise residential buildings, gated communities, shopping malls, airport terminals, business parks) into the trial. Each unit was randomized to either the intervention or control group; in each unit, volunteer lay responders (e.g., office staff, sales clerks, security guards and neighborhood volunteers) were trained to recognize OOH-CA, access 911 or its equivalent, and administer CPR. Intervention units were also equipped with AEDs, and lay responders in the intervention group were taught to use an AED while awaiting the arrival of EMS personnel. In addition to the primary outcome of survival to hospital discharge, OOH-CA victims in each of the two groups were compared with respect to Utstein criteria (a set of standardized process and outcome variables used in cardiac arrest studies), neurological status, quality of life, resource use and associated costs (22, 23).

In August 2004, the results of this seminal study were published in the *New England Journal of Medicine* (24). Patients with treated out-of-hospital cardiac arrest in the intervention and control groups were similar in age, gender, and frequency of witnessed event. Survival was roughly double in the intervention group: 30 survivors among 130 arrests in the AED group vs. 15 survivors among 107 arrests in the CPR-only group ($p=0.03$; relative risk = 2.0; 95% CI = 1.07–3.77). The effectiveness of public access defibrillation was limited to public places; survival from OOH-CA in residential facilities was very rare and was identical in the intervention and control groups: 1 survivor among 33 arrests in the AED group vs. 1 survivor among 37 arrests in the CPR-only group. There was no difference between the intervention and control groups in the measured neurological status of survivors. There were no serious adverse events to patients or to lay responders.

The PAD Trial results support the concept that trained volunteers can use AEDs safely and effectively in a variety of public locations. However, public access defibrillation was not a successful strategy in residential facilities, where more than 80% of OOH-CAs occur. The ineffectiveness of the residential PAD programs is attributed to delays in discovering OOH-CA victims who are alone at home when the arrest occurs, compared to the almost immediate identification of a collapsed victim in public locations.

Cost-effectiveness should be carefully considered if PAD programs are to be widely implemented. The incremental cost-effectiveness of volunteer lay-responder defibrillation varies with the frequency of cardiac arrest. "Hypothetical" computations regarding program cost can be performed from a facility's perspective, using assumptions based on data collected during the PAD Trial. An "average" PAD trial facility wishing to implement a PAD program would need about 3 AEDs and 14 volunteers to maintain a reasonable capability for responding to episodes of cardiac arrest (25). The training/retraining costs average \$25 per volunteer per year for a CPR-only program and \$50 per year for an AED program, and the cost of purchasing and maintaining an AED is \$3,000 over 5 years (the average annual cost is \$600 per AED ≥ \$1,800/yr for 3 AEDs). The CPR-only program would cost about \$350 per year compared to \$2,500 per year for a PAD program. This assumes that no additional equipment or infrastructure is needed and considers only direct costs to the facilities; potential societal costs/benefits such as hospitalization or EMS usage costs are not included .

The incremental cost effectiveness of a PAD program relative to a CPR-only program (i.e., the cost per additional life saved) can be calculated as the difference between the annual CPR-only and AED costs ($2,150 in this example) divided by the difference in the annual expected number of survivors. As the latter may vary substantially, so may the incremental cost effectiveness. The table illustrates this variability for facilities experiencing different frequencies of cardiac arrest and for a range of possible survival rates associated with a PAD program. Based on the PAD Trial results, survival in the CPR-only program is assumed to be half that of a PAD program. In this example, incremental costs of a PAD program, relative to CPR-only, could range from $7,167 to $430,000 per additional life saved by PAD, depending upon the frequency of cardiac arrest at the location where the program is implemented.

Thus, even though the PAD Trial has demonstrated a positive impact on survival from OOH-CA in public locations, the cost-effectiveness of PAD programs depends upon implementing them in facilities where cardiac arrests are relatively frequent—at least 1 OOH-CA every two years.

TABLE

*Hypothetical Incremental Program Cost-Effectiveness of PAD**

Number of cardiac arrests occurring at facility	Survival rate with AED + CPR[†]		
	10%	20%	30%
1 per 10 years	$430,000	$215,000	$143,333
1 per 5 years	$215,000	$107,000	$ 71,667
1 per year	$ 43,000	$ 21,500	$ 14,333
2 per year	$ 21,500	$ 10,750	$ 7,167

*Cost of each additional life saved computed as:

(average yearly AED+CPR cost – average yearly CPR-only cost)

(expected #AED+CPR survivors/yr – expected #CPR-only survivors/yr)

[†] Assumes survival is doubled with a community-based CPR+AED program, compared to a CPR-only program.

Vasopressin for Asystole and Refractory OOH-CA

Historically, epinephrine has been the first-line drug for treatment of cardiac arrest. The role of epinephrine has been repeatedly codified in the AHA Emergency Cardiac Care Guidelines, most recently in 2000 (26). In January of 2004, the European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group published the results of a randomized, double-blinded, controlled trial comparing epinephrine to vasopressin in the treatment of out-of-hospital cardiac arrest (27). This seminal study not only challenged the role of epinephrine in cardiac arrest treatment algorithms, but also highlighted the limitations of relying upon published guidelines, particularly in the area of cardiac arrest resuscitation.

Vasopressin is a naturally occurring antidiuretic hormone, which in very high doses acts as a noradrenergic peripheral vasoconstrictor. In the early 1990s, Lindner et al. observed that the concentration of endogenous vasopressin was higher in survivors of cardiac arrest than in those who had no return of spontaneous circulation (ROSC) (28). Subsequent laboratory and animal studies demonstrated that during cardiac arrest, vasopressin increases blood flow to vital organs, improves cerebral oxygen delivery, increases chances of resuscitation and improves neurological outcomes in survivors (29–33). Furthermore, it had been noted that vasopressin retains its vasoactive properties in the presence of severe hypoxia and acidosis, a characteristic not shared by epinephrine (34). A small clinical study comparing vasopressin to epinephrine in the treatment of V-fib arrest found increased ROSC with no increased survival to hospital discharge (35). These promising results prompted the design of a large-scale clinical trial to evaluate the efficacy of vasopressin in cardiac arrest.

The European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study was conducted using 44 participating physician-staffed ambulances in 33 communities in Austria, Germany and Switzerland (27). Adult patients with OOH-CA presenting with ventricular fibrillation, asystole or pulseless electrical activity (PEA) that required CPR and drug therapy were randomized to receive either epinephrine (1 mg doses) or vasopressin (40 IU doses). Patients who were resuscitated by defibrillation alone were excluded from the study, as were individuals with documented terminal illness, cardiac arrest after trauma, hemorrhagic shock, pregnancy, no intravenous access, age less than 18 years, or a do-not-resuscitate order.

The study drugs were supplied in identical packaging; patients, providers and investigators were blind to which drug was received until after analyses were completed. The protocol specified intravenous injection of the study drug, followed by 20 cc of normal saline, to be repeated after three minutes if there was no ROSC. Treating physicians were then free to give additional doses of epinephrine at their discretion and any other drug therapy they thought appropriate. The primary endpoint was survival to hospital discharge; interim endpoints were also recorded.

During the 33-month study period, 1,219 patients were randomized; for 33 patients the drug codes were missing, leaving 1,186 patients in the main analysis. Of this total, 589 patients were randomized to the vasopressin group and 579 received epinephrine. There were no significant differences between the two groups with respect to age, gender, comorbidities, pre-existing cardiovascular disease, frequency of witnessed arrest or bystander CPR or EMS response times. The arrest rhythm was V-fib in 472 cases (39.8%); asystole in 528 cases (44.5%) and PEA in 186 cases (15.7%).

Chi-square testing was used to determine differences between the vasopressin group and the epinephrine group for primary and secondary endpoints. For patients with ventricular fibrillation or PEA, there were no significant differences between those treated with vasopressin and those treated with epinephrine. For patients who presented in asystole, those who received vasopressin were significantly more likely to survive to hospital admission (29.0% vs. 20.3%; p=0.02) and to hospital discharge (4.7% vs. 1.5%; p=0.04) compared to those who received epinephrine.

There were 732 patients who had no ROSC after administration of two doses of the study drug and received further doses of epinephrine. Among these patients, those who had initially received vasopressin were significantly more likely to survive to hospital admission (25.7% vs. 16.4%; p=0.002) and to hospital discharge (6.2% vs. 1.7%; p=0.002) compared to those who were in the epinephrine treatment group. These survivors of refractory arrest were similar to other survivors in cerebral performance at hospital discharge.

The authors acknowledge that because care in the emergency department (ED) and in the hospital was not standardized, outcomes could have been affected. However, in addition to the findings regarding vasopressin, the study confirmed all of the previously documented predictors of survival. Multivariate analysis revealed that, as expected, survival was higher for patients with witnessed arrest, and for those who received basic life support (BLS) within 10 minutes, or amiodarone or fibrinolysis prior to arrival in the emergency department. Given the blinding, it is difficult to explain why the study would confirm all of the previously documented predictors of survival while producing spurious results regarding the study drug. These findings substantially enhance the credibility of the study results.

Although the study failed to prove the primary hypothesis (i.e., vasopressin improves survival in V-fib arrest), it clearly demonstrated that vasopressin is similar to epinephrine for V-fib and PEA in OOH-CA. More important, it demonstrated that vasopressin is superior to epinephrine for OOH-CA due to asystole, and that the combination of vasopressin and epinephrine is superior to epinephrine alone for refractory OOH-CA.

When the American Heart Association published its emergency cardiac care (ECC) guidelines in 2000 (26, 36), the European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study was already underway and expected to show benefit. Vasopressin was included in the V-fib algorithm as "Type II b" (acceptable, fair evidence) and rated as "Indeterminate" for asystole and PEA. When the study was published in January 2004, the next planned revision of the ECC Guidelines was more than a year away. The *New England Journal of Medicine* editorial that accompanied the article argued that "these advances should be translated into a new standard of care without delay" (37). The editorial called upon the AHA to issue "an interim guideline incorporating these important new therapeutic advances," a call which, thus far, has gone unheeded. It may be incumbent upon medical policymakers to facilitate the implementation of new guidelines when scientific advances are made, but practical considerations limit the frequency with which new guidelines can be developed. This is especially true of the advanced cardiac life support (ACLS) treatment algorithms. Thus, physicians who manage OOH-CA need to remain aware of published literature and to incorporate, when appropriate, the results of clinical trials into their practice during the five-year intervals between formal promulgation of ECC guidelines.

Alternative CPR Techniques and Devices

Cardiopulmonary resuscitation is the mainstay of basic life support and a critical link in the American Heart Association's "chain of survival" (38). Researchers continue to investigate optimal parameters for CPR as well as the usefulness of alternative techniques and devices.

Compression:Ventilation Ratios

As a significant determinant of survival after cardiac arrest, coronary perfusion pressure must be maintained during CPR and minimized during interruptions of chest compression for ventilation (39, 40). Current AHA guidelines recommend 15 compressions for every 2 ventilations (15:2), a change in the year 2000 from 5 compressions for every 1 ventilation (5:1) (36). In an effort to simplify BLS skill acquisition and retention, researchers in Great Britain have emphasized chest compressions in their algorithm and advocated a ratio of 50:5 (41, 42). A recent experimental animal study showed improved 24-hour neurological function in animals that received 4 minutes of chest compressions alone followed by 8 minutes of 100:2 when compared to standard CPR, with no significant difference noted between the two groups in coronary perfusion pressure and vital organ blood flow (43). At this time, the optimum compression:ventilation ratio remains unclear.

Compression-Only CPR

If reasonable oxygen saturation persists after 10 minutes of chest compressions, is there a need for ventilation initially during CPR? A growing body of evidence shows no significant change in coronary perfusion pressure, vital organ blood flow, 24-hour survival and ROSC in animal studies with compression-only CPR compared with standard CPR (44). Reluctance to perform mouth-to-mouth ventilations by bystanders, BLS instructors, nurses and physicians has been documented in anonymous surveys (45–47). Bystanders are already performing compression-only CPR. In one observational study where pre-hospital personnel documented standard CPR, compression-only CPR and no CPR by bystanders at the scene, no significant difference was noted in long-term survival between standard and compression-only CPR (48). In a Seattle study of telephone-dispatcher-assisted BLS, where callers were randomized to standard CPR or compression-only CPR instruction, no difference in rate of survival to hospital discharge was observed (49).

Compression Rates

Chest compressions at a rate greater than 100 per minute (high-frequency CPR) have shown improved vital organ blood flow and 24-hour survival in animal studies (50, 51). Controlled clinical studies are lacking, but experimental human models demonstrate improved hemodynamics when compared to standard CPR (52, 53). AHA guidelines do not recommend this modality at present, citing the need for controlled human trials (36).

Interposed Abdominal Compression/Cardiopulmonary Resuscitation

Commonly referred to as "IAC-CPR," this technique involves compression of the abdomen in alternation with chest compression during resuscitation. The technique was first described in 1957 (54) and suggested as an adjunct to standard CPR in 1981 (55). Using overlapping hands or hands placed side by side (56), compression is applied to a point midway between the xiphoid process and umbilicus, in an effort to generate at least 100 mm Hg of force on the abdominal aorta during the relaxation phase of chest compression; this is the amount of force required to palpate the aortic pulse when the heart is beating normally (36).

Statistically significant improvements in outcomes have been shown in three randomized clinical trials of IAC-CPR for in-hospital cardiac arrest (57–59). The largest of these trials demonstrated a significant difference in ROSC (51% vs. 27%) and survival to hospital discharge (25% vs. 7%) in patients randomized to the IAC-CPR treatment group versus the standard CPR group (59). A single pre-hospital study of IAC-CPR reported no significant improvement in outcome but no increase in complications (60). IAC-CPR appears to be safe; there have been no reports of increased emesis or aspiration (61).

Mechanical CPR

Mechanical chest compressors can be manual or automatic. With this modality, the body of a patient is placed over a backboard, with the sternum under a mechanical piston, which is programmed to a set compression depth and rate. Several variations of this device are commercially available and some have achieved widespread use. In most cases, key hemodynamic variables are similar to, or worse than, those measured during standard CPR (62). Currently available devices remain in contact with the chest wall throughout resuscitation, preventing the natural recoil of the chest wall during relaxation and thus impeding venous return to the heart. Clinical outcome studies have not shown improvement in survival outcome, and higher rates of rib and sternal fractures have been noted (63). Thus, mechanical compression devices are recommended only in the absence of adequate personnel or in transport situations that make standard CPR difficult.

Active Compression-Decompression CPR

The term "active compression-decompression CPR" (ACD-CPR) refers to the use of a mechanical device attached to a patient's sternum by suction, which is used to actively push down and pull up the patient's chest wall during resuscitation. Based on the thoracic pump model of mechanical blood flow, the additional negative intrathoracic pressure generated by active decompression theoretically increases venous return when compared to standard CPR. Experimental data from human and animal studies have demonstrated higher perfusion pressures with ACD-CPR (64–66), though clinical trails have been inconsistent. Two randomized, controlled pre-hospital trials from France demonstrated significant improvement in survival to hospital discharge without neurologic impairment, and in 1-year survival (67, 68). However, because of methodologic flaws in these studies, reviewers from the latest Cochrane database review have concluded that ACD-CPR is not associated with clear benefit for patients with cardiac arrest, and a higher incidence of rib fractures has been noted in some studies (69, 70).

Phased Thoracic-Abdominal Compression-Decompression CPR

Phased thoracic-abdominal compression-decompression (PTACD) CPR combines the techniques of interposed abdominal compression CPR (IAC-CPR) and active compression-decompression CPR (ACD-CPR). A device that attaches by adhesive to the sternum and abdomen is used to apply compressions and active decompressions. Outcome measures of coronary perfusion pressures and 48-hour survival in animal studies showed significant improvement with PTACD-CPR when compared to standard CPR (70, 71). A single human trial that compared PTACD-CPR to standard CPR demonstrated no improvement in ROSC or survival to hospital discharge, though a subgroup analysis suggested a potential benefit for patients with an initial rhythm of asystole or pulseless electrical activity (72). Fewer complications have been noted with PTACD-CPR regarding rib fractures. The Food and Drug Administration has not approved PTACD-CPR devices for use, pending further studies.

Vest CPR

A sealed vest that rhythmically inflates and deflates around the thorax has been reported to promote increased blood flow and 24-hour survival in animal studies (73, 74). Three clinical studies have shown higher coronary perfusion pressure, increased rates of ROSC, and improved 6-hour survival, but no significant improvement in rate of hospital discharge (36, 75, 76). Barriers to the use of this device include both the time needed to train and limited vest sizes, which currently are only available for patients in the 40–50 kilogram range. A smaller device, in the form of a pneumatic band, has been used successfully with pigs (77). Additionally, lighter models are being developed, which include means to ventilate and defibrillate during resuscitation (78). Complications from vest CPR have not been reported. A multi-center, randomized controlled trial of this device is currently in progress.

Impedance Threshold Valve

The impedance threshold valve (ITV) device is designed to increase venous return to the heart during CPR. The ITV is placed between the ventilation bag and endotracheal tube or mask; during the relaxation phase of chest compression, the valve prevents air entry into the lungs, increasing negative intrathoracic pressure and venous return. Positive pressure ventilation through the valve can be provided during resuscitation without significant resistance, but must be removed once ROSC has occurred.

Two animal studies demonstrated significantly increased vital organ blood flow and coronary perfusion pressure when ITV was combined with standard CPR (79) and with ACD-CPR (80). One pre-hospital clinical trial of ACD-CPR with ITV showed significant increases in end-tidal carbon dioxide, coronary perfusion pressure and diastolic arterial pressure when compared to ACD-CPR alone (81). No complications or outcome studies regarding long-term survival have been reported.

Invasive CPR

Little data exists to support open cardiac massage at this time. A single animal study showed improved 7-day survival with open cardiac massage after ineffective closed-chest CPR in cardiac arrest (82). Five uncontrolled observational studies (83–87) have failed to demonstrate improvement in long-term survival, although one trial showed improved ROSC (83). Current AHA guidelines support the consideration of open cardiac massage under special circumstances only, including cardiac arrest caused by hypothermia, pulmonary embolism or pericardial tamponade; chest deformity where closed-chest CPR is ineffective; and penetrating trauma with cardiac arrest (36). When applied late (> 25 minutes of total arrest time), this technique has not shown improvement in outcome (84), so it should not be used as a "last-ditch" effort. Other invasive measures include cardiopulmonary bypass and extracorporeal membrane oxygenation, intra-aortic balloon pump, and left ventricular assist devices, though as with open cardiac

Key Concepts

1. Public access defibrillation programs have been shown to improve survival of cardiac arrest patients treated in public places but not in residential settings.
3. The cost effectiveness of PAD programs depends on the frequency of cardiac arrest at the location where the program is implemented.
4. Vasopressin is superior to epinephrine in the initial treatment of asystolic cardiac arrest and is equivalent to epinephrine in the initial treatment of V-fib and PEA.
5. Vasopressin in combination with epinephrine improves outcome of refractory OOH-CA compared to epinephrine alone.
6. There is evidence to support the use of compression-only CPR, intra-abdominal compression CPR, and active compression-decompression devices, although large-scale trials are needed to demonstrate their effectiveness for OOH-CA.

massage, these measures require a highly trained, well-coordinated, multidisciplinary team.

A newer modality, minimally invasive direct cardiac massage (MIDCM), provides internal cardiac massage without formal thoracotomy. A padded plate is passed through a 3–4 cm incision in the medial aspect of the left fourth or fifth intercostal space, opened within the thoracic cage; the padded plate is used to compress the heart against the vertebrae. Animal and human studies demonstrated higher perfusion pressures when compared with external compressions (88-90). In one clinical pre-hospital study, MIDCM was associated with ROSC in 7 of 25 patients, none of whom survived to hospital discharge (91).

Summary of Alternative CPR Techniques and Devices

In the pre-hospital setting and in the absence of a shockable rhythm, traditional CPR remains the best available technique. Compression-only CPR may prove to be valuable when bystanders hesitate to provide ventilation at the risk of disease communication. IAC-CPR has shown significant improvement in mortality and, unlike many of the other alternative CPR modalities, does not require extensive training or additional equipment. While ACD-CPR has shown promise, pooled analysis of current data has demonstrated no significant difference in mortality (69). In the future, large-scale randomized trials of ACD and vest devices may provide evidence of significant benefit.

Conclusions

Recently published reports suggest new approaches to decrease mortality from out-of-hospital cardiac arrest. The PAD Trial, a randomized, controlled trial of public access defibrillation, demonstrated that an organized program to train and equip laypersons to respond to OOH-CA with CPR and AEDs significantly increased survival to hospital discharge compared to a program using CPR alone, in non-residential settings. The European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study, a randomized, controlled, double-blinded trial that compared vasopressin to epinephrine in the treatment of OOH-CA, demonstrated that vasopressin is superior to epinephrine for the initial treatment of asystolic arrest, and that the combination of vasopressin and epinephrine is superior to epinephrine alone in the treatment of refractory out-of-hospital cardiac arrest. There is evidence to support the use of compression-only CPR, intra-abdominal compression CPR, and active compression-decompression devices, although large-scale trials are needed to demonstrate their effectiveness for OOH-CA.

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Unstable Angina and Non-ST-Segment Myocardial Infarction:

An Evidence-Based Approach to Management

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Abstract

Unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) represent two common, closely related acute coronary syndromes with potentially high morbidity and mortality. Integration of information from the history, physical exam, electrocardiogram, and cardiac biomarkers is used to formulate both the diagnosis of UA/NSTEMI and the overall assessment of patient prognosis and risk. Early diagnosis and risk stratification of patients with UA/NSTEMI enable the physician to initiate timely, appropriate treatment. (There is strong clinical evidence supporting the tailoring of specific therapies to the risk profile of the patient.)

In recent years, powerful new medical and invasive therapies have been developed. Pharmaceutical agents for UA/NSTEMI may be broadly grouped into one of three categories: anti-ischemic, anti-platelet, and anti-thrombotic agents. Standard therapy for UA/NSTEMI has commonly included oxygen, aspirin, nitrates, morphine, beta-blockers and heparin. Potent new anti-platelet agents, including inhibitors of platelet adenosine diphosphate and glycoprotein IIb/IIIa receptors, play important, expanding roles in the management of these syndromes. Low-molecular-weight heparins have been shown to be an effective alternative to unfractionated heparin in their treatment. Major advances in invasive techniques and devices over the last decade include revascularization with percutaneous coronary intervention and drug-eluting intracoronary stents. Strong interest exists in studying the potential benefits and risks associated with an early invasive therapeutic strategy rather than an aggressive medical regimen for patients with UA/NSTEMI.

As new treatments are rapidly added to our growing arsenal of management options, clinicians are constantly challenged with incorporating complex new information and guidelines into their practices in a timely fashion. To assist clinicians with this challenge, this article will review the evidence to support the use of current therapeutic options for UA/NSTEMI, with an emphasis on summarizing the most recent clinical guidelines jointly published by the American College of Cardiology and the American Heart Association.

Key Words: Acute coronary syndrome, coronary artery disease, myocardial infarction, unstable angina.

Introduction

UNSTABLE ANGINA (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) represent two common, closely related acute coronary syndromes with potentially high morbidity and mortality. Early diagnosis and risk stratification of patients with UA/NSTEMI enable the physician to initiate appropriate new medical and invasive therapies. However, as "state of the art" treatments are rapidly added to the growing arsenal of management options, clinicians are constantly challenged with incorporating complex new clinical pathways and guidelines into their practices. To aid clinicians in navigating through these recent advances, this article will provide an updated, evidence-based review of currently available therapeutic options, with an emphasis on summarizing and explaining the most current clinical practice guidelines addressing the management of UA/NSTEMI.

Published practice guidelines help to standardize the assessment and treatment of UA/NSTEMI patients. In 1994, the Agency for Healthcare Policy and Research (AHCPR) published evidence-based guidelines for the management of patients with UA and NSTEMI (1). The AHCPR guidelines were succeeded in 2000 by a joint publication from the American College of Cardiology (ACC) and the American Heart Association (AHA). In 2002, the ACC/AHA guidelines of year 2000 were updated (2). These comprehensive recommendations incorporated several important new clinical studies published or presented after the original year 2000 guidelines were developed. The evidence classification system used by the ACC and AHA in developing their recommendations will be noted in parentheses throughout this article.

Epidemiology

Ischemic heart disease is one of the leading causes of death in the United States; it accounted

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for more than 20% of a total mortality of 2,443,387 in 2002 (3). UA and NSTEMI are two highly prevalent, potentially life-threatening manifestations of this disease, accounting for a total of 1,295,000 hospital admissions in the US in 2001; 56% of these patients were 65 years of age or older, and 41% were women in all age groups (4). The number of US patients with a primary diagnosis of coronary atherosclerosis more than doubled during the 1990s, and the total over 65 years of age more than tripled (5).

Patients with coronary artery disease (CAD) frequently present to the emergency department (ED), often without a previous diagnosis and with a new onset of symptoms. In 2002 a total of 5,637,000 US ED visits were for chest pain and related symptoms, accounting for approximately 5% of total visits (6).

Definitions

"Acute coronary syndrome" (ACS) is a term describing any array of clinical symptoms resulting from underlying acute myocardial ischemia. ACS encompasses a wide spectrum of clinical entities, including unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). These conditions represent a continuum of generally increasing severity and risk, with differences in etiology, pathophysiology, presentation, and management.

Angina may be categorized as a stable chronic condition or as an ACS, based upon the pattern, timing, and severity of symptoms. Angina is classified as unstable when a patient experiences prolonged symptoms at rest, severe new onset angina, or episodes that are more frequent or prolonged (7). UA and NSTEMI are closely related syndromes sharing similar pathophysiology and clinical presentation, but NSTEMI presents with an increased severity and risk. Specifically, NSTEMI is distinguished from UA by the presence of an elevation in serum biochemical markers of myocardial necrosis and infarction. However, from a practical standpoint, clinicians may not be able to readily differentiate between patients with UA and those with NSTEMI at the time of initial presentation, due to the delayed release profile of most biochemical cardiac markers and constraints in obtaining timely laboratory values. Therefore, UA and NSTEMI are frequently considered together as the same clinical syndrome in discussions about initial diagnosis and treatment. Finally, STEMI is similar in presentation to NSTEMI, but is defined by the additional presence of ST elevation on the electrocardiogram (ECG) (2).

Etiology / Pathophysiology

The fundamental etiologic mechanism shared by all the forms of ACS is an imbalance between myocardial oxygen supply and demand. The most common cause of ACS is thrombus formation over a preexisting atherosclerotic plaque that has undergone disruption or erosion. Plaques vulnerable to disruption and thrombosis formation commonly have a large lipid core with elevated tissue factor content, a thin fibrous cap, and enhanced inflammatory activity within the plaque. When endothelial erosion of a plaque occurs, the subendothelial connective tissue is exposed, allowing platelets to adhere and eventual thrombus to form at the plaque surface. Alternatively, during plaque disruption, the fibrous cap tears or fissures to expose the highly thrombogenic lipid core to arterial blood, leading to platelet aggregation and thrombus formation. When there is blood vessel wall damage or plaque rupture, a monolayer of platelets adheres to the exposed subendothelial matrix either directly or with von Willebrand factor. The next step is platelet activation, which may be triggered by platelet adhesion or by exposure to a number of different chemical agonists, including collagen, thromboxane A2, thrombin, adenosine diphosphate (ADP), and epinephrine. Platelet activation initiates a chain of complex events, including the expression and activation of glycoprotein (GP) IIb/IIIa receptors on the platelet surface. The final common pathway leading to thrombus formation is platelet aggregation, which is mediated by the GP IIb/IIIa receptors. Fibrinogen bridges the activated platelets by binding to two GP IIb/IIIa receptors. The result is the formation of a platelet-fibrin hemostatic plug, which may propagate into either an occlusive or nonocclusive thrombus (8).

In UA and NSTEMI, the intra-arterial thrombus does not fully occlude the lumen, and some antegrade blood flow remains intact. However, clumps of activated platelets at the surface of an intra-luminal thrombus as well as components of the disrupted plaque may be swept downstream into the distal myocardial vascular bed. These microemboli may cause microscopic foci of myocardial necrosis and are believed to be primarily responsible for the release of biomarkers of myocardial infarction seen in patients with NSTEMI (9). The contrasting scenario is for the thrombus to fully occlude the arterial lumen, resulting in an acute Q-wave myocardial infarction (commonly with ST elevation). UA/NSTEMI primarily caused by a nonocclusive thrombus benefit from a treatment regimen including anti-thrombotic and antiplatelet agents (10). This form of UA/NSTEMI is by far the most common and therefore will be the focus of discussion in the rest of this article.

Other less common causes of UA/NSTEMI include: (a) dynamic obstruction resulting from spasm of epicardial or intramural coronary arteries, (b) progressive mechanical obstruction, as seen with severe atherosclerotic narrowing in the absence of thrombus or with restenosis following percutaneous coronary intervention (PCI), (c) inflammatory or possibly infectious processes, and d) secondary conditions that are extrinsic to the coronary vessels. In many cases, multiple causes contribute to the development of ACS (10).

Diagnosis

Given the possible complexities in establishing an early and accurate diagnosis of ACS, it is important for the clinician to use all available information, including the history, physical exam (PE), electrocardiogram (ECG), and cardiac biomarkers, to formulate both the diagnosis of UA/NSTEMI and the overall assessment of patient prognosis and risk. The initial evaluation of a patient with potential ACS should begin with determining the likelihood that a patient's clinical presentation represents ACS due to obstructive CAD. Simultaneously, the patient's risk of an adverse outcome such as death, MI, or recurring severe ischemia should be assessed. This risk strongly correlates with the patient's likelihood of ACS secondary to CAD. The 2002 ACC/AHA guidelines provide a proposed system to aid in the diagnosis and risk stratification of patients with possible UA/NSTEMI (2). The significant elements of the history, physical examination (PE), ECG, and cardiac biomarkers will be discussed in the following sections.

Clinical History and Physical Examination

Angina is typically defined as a deep, poorly localized chest or arm discomfort that is reproduced with strenuous activity and relieved with rest or nitroglycerin. Some patients may present atypically with no component of chest pain but only jaw, neck, arm, or epigastric discomfort. Others may complain solely of associated symptoms, including dyspnea, nausea, vomiting, diaphoresis, syncope, dizziness, and generalized weakness or fatigue. These symptoms are commonly referred to as "anginal equivalents" (2).

In addition to obtaining historical details about the nature of a patient's symptoms, clinicians should also inquire about any prior history of CAD and MI and the presence or absence of traditional CAD risk factors such as hypertension, hypercholesterolemia, smoking, diabetes, and family history of premature CAD. It should be noted, however, that many of these traditional risk factors have been shown to be only weakly predictive of the likelihood of acute myocardial ischemia and should be used in combination with other diagnostic findings to determine the probability of an ACS (11 – 13).

The physical examination is of limited value in the diagnosis of UA/NSTEMI; however, it is particularly useful in assessing for possible hemodynamic complications resulting from ACS, co-morbidities, precipitating causes, and evidence of alternative diagnoses. Patients with signs of left ventricular dysfunction, cardiogenic shock, or acute mitral regurgitation have a much higher likelihood of significant CAD and poorer outcomes. The presence of bruits or pulse deficits may indicate significant underlying peripheral or cerebrovascular disease, both of which increase the probability of concurrent CAD and future risk.

Electrocardiogram

The ECG is essential in the diagnosis, risk assessment, and treatment of patients with potential ACS. The ACC/AHA guidelines recommend that a 12-lead ECG be obtained within 10 minutes of presentation for patients with ongoing chest pain and as rapidly as possible for all other patients with probable ACS (Class I, Level C) (2). For a patient with possible UA/NSTEMI, certain ECG findings may predict the likelihood of ACS as well as patient prognosis. Dynamic ST-segment changes greater than or equal to 0.05 mV (0.5 mm), which develop with rest angina and resolve with the patient's symptoms, are strongly suggestive of severe CAD with coronary thrombus formation and a high level of risk (14). Deep pre-cordial T-wave inversions greater than or equal to 0.2mV (2 mm) also predict a poorer prognosis and may reflect a critical stenosis of the left anterior descending coronary artery (15). Nonspecific ST-segment (less than 0.05 mV) and T-wave (less than 0.2 mV) changes have a lower predictive value (16).

It should be emphasized, however, that a normal ECG does not exclude the possibility of an ACS, as it is a relatively insensitive test. One large study analyzed patients with chest pain and an initially normal or nonspecific ECG, and reported an overall probability of NSTEMI of 3%, with a range from less than 1% to 17% depending on the patient's age, sex and symptom characteristics (17). A normal or nonspecific ECG does, though, provide helpful prognostic information. Patients with a confirmed AMI but a nondiagnostic presenting

ECG have been shown to have a lower risk of death or serious complications as compared to those with significant ECG abnormalities (16, 18, 19).

Biochemical Cardiac Markers

Biochemical cardiac markers are intracellular macromolecules released and detectable in the peripheral circulation when myocardial necrosis is present. They should be measured in all patients presenting with probable ACS. Three widely used markers are the cardiac troponins, creatine kinase-MB (CK-MB), and myoglobin. Cardiac troponins are generally considered to be the biomarkers of choice. Currently available assays for cardiac troponins I and T have high sensitivities, with the ability to detect even microscopic areas of necrosis that are undetectable by CK-MB measurements, and they have nearly absolute myocardial tissue specificity. If troponin testing is not available, the best alternative is CK-MB measurement by mass assay, which has a lower sensitivity and specificity compared to the assays for cardiac troponins. Myoglobin measurement is a highly sensitive but very nonspecific test for identifying early cardiac necrosis and should therefore be used in conjunction with either a cardiac troponin or CK-MB. Due to their delayed release profiles, the cardiac troponins and CK-MB have a lower sensitivity for the early detection of myocardial infarction. Therefore, for patients with initially negative cardiac markers within six hours of symptom onset, a repeat measurement should be performed 8 to 12 hours after the onset of symptoms (2, 20).

Due to the availability of highly sensitive troponin assays, the ACC and the Joint European Society of Cardiology have recently proposed a revised definition of acute myocardial infarction (AMI) that requires a diagnostic rise and fall in cardiac biomarkers (troponin or CK-MB) in addition to either ischemic symptoms or significant ECG changes (21). On the other hand, unstable angina, by definition, cannot be identified or excluded by any available biochemical marker of myocardial necrosis (20).

In addition to their role in identifying and defining AMI, cardiac markers also provide important prognostic information (22–24). NSTEMI patients with elevated troponin values have a higher risk of death or future MI compared with both troponin and CK-MB negative patients (25). This risk increases proportionately with the quantity of troponin measured (26, 27). A similar risk relationship has been shown with increasing levels of CK-MB (28). As will be discussed in later sections, high-risk ACS patients who present with elevated cardiac troponin levels have also been shown to receive a greater benefit from certain treatments, including GP IIb/IIIa inhibitors, low molecular weight heparin (LMWH), and interventional revascularization (29–34).

Risk Stratification

Early risk stratification of patients with UA/NSTEMI involves integrating relevant information from the history, PE, ECG, and biochemical cardiac marker measurements as discussed above. This estimate of both short- and long-term risk is a key component in the formulation of management decisions involving disposition and choice of inpatient care level, as well as selection of treatment and necessary additional diagnostic testing. Risk assessment is also an ongoing process requiring the possible reclassification of a patient's risk category as additional clinical information becomes available during the course of a patient's hospitalization. Using multivariable regression techniques applied to several recent large trials, various systems have been proposed to assist clinicians in estimating an ACS patient's risk profile (35–37).

The Thrombolysis in Myocardial Infarction (TIMI) risk score (Table 1) for UA/NSTEMI is a 7-point system developed by Antman et al. (37), which predicted a patient's risk for death, non-fatal MI, or severe ischemia requiring urgent revascularization, at 14 days after presentation. This clinically practical prognostic tool was derived from and validated in the TIMI 11B (38) and ESSENCE trials (39). It has subsequently been validated in two other large trials (34, 40).

In addition to its application to higher risk patients selected into clinical trials, the TIMI risk score has been successful in accurately predicting death and other adverse cardiovascular outcomes in a general, lower risk population of unselected patients with UA/NSTEMI (41). Recent studies

TABLE 1
TIMI Risk Score Variables

- Age greater than 65 years
- Presence of at least three traditional risk factors for CAD (male sex, family history, hyperlipidemia, diabetes, smoking, hypertension, obesity)
- Prior coronary stenosis > 50%
- Use of aspirin within the previous seven days
- Presence of ST-segment deviation on admission ECG
- At least two anginal episodes in the prior 24 hours
- Elevated serum biochemical cardiac markers

Each variable above is assigned 1 point. Risk score is equal to a summation of the points (0–7).

have also demonstrated a progressively greater benefit for higher risk groups from newer available therapies for UA/NSTEMI, including GP IIb/IIIa inhibitors (40), LWMH (38, 39), and early invasive treatment (34).

Treatment

Management of UA/NSTEMI should be centered on the immediate relief of myocardial ischemia and the prevention of significant adverse outcomes. Pharmacological therapies may be broadly grouped into one of three categories: anti-ischemic, anti-platelet, and anti-thrombotic agents. Invasive treatments include revascularization with PCI or coronary artery bypass grafting (CABG).

"Standard" therapy for UA/NSTEMI has commonly included oxygen, aspirin, nitrates, morphine, beta-blockers and heparin. In recent years, there have been many advances in our understanding of the pathophysiology of ACS including an evolving knowledge of the intricate and important role of platelets in coronary thrombus formation. As a result, current management strategies have focused on the appropriate utilization of newer classes of potent anti-platelet agents, including inhibitors of platelet ADP and GP IIb/IIIa receptors. Recent clinical research has also evaluated the role of low molecular weight heparins (LMWH) in the treatment of ACS. Additionally, there has been strong interest in studying the potential benefits and risks associated with employing an early invasive therapeutic strategy compared with an aggressive medical regimen for patients with UA/NSTEMI.

Anti-ischemic Therapy

The following agents are administered to decrease myocardial ischemia by either reducing myocardial oxygen demand or increasing its supply.

Oxygen. Theoretically, supplemental oxygen may limit ischemic myocardial injury by increasing the myocardial oxygen supply. However, supplemental oxygen has not been shown to reduce morbidity or mortality associated with UA/NSTEMI. As a result, the ACC/AHA guidelines recommend providing supplemental oxygen only to patients with signs of respiratory distress or arterial hypoxemia, with the goal of maintaining oxygen saturation above 90% (Class I, Level C) (2).

Nitrates. The primary physiological action of nitrates is vasodilation of veins, arteries, and arterioles through the relaxation of vascular smooth muscle. Venodilation results in a decrease in preload, which in turn causes a reduction in ventricular wall stress and myocardial oxygen demand. To a lesser degree, nitrates also reduce afterload via dilation of the arterial system. However, the beneficial effects on myocardial oxygen demand may be partially counteracted by reflex increases in heart rate and contractility if a beta-blocker is not concurrently given. In addition to these hemodynamic effects, nitrates directly dilate the epicardial coronary arteries and smaller arterial vessels, resulting in improved blood flow and oxygen delivery to ischemic areas (2).

A majority of studies on nitrate use in UA have been small and uncontrolled and have focused on symptom relief and the prevention of recurrent ischemia (42–46). All of these trials have shown a reduction in the frequency and/or severity of anginal symptoms with the administration of nitroglycerin to UA patients.

There are, however, no strong data supporting the potential benefit of nitrates in improving patient prognosis. A review of small studies conducted during the prethrombolytic era concluded that there was a 35% reduction in mortality rates with the use of intravenous nitrates in AMI (47). In contrast, two recent, large, randomized trials demonstrated that the use of nitrates in suspected AMI patients failed to significantly reduce mortality (48, 49).

The ACC/AHA guidelines recommend nitrates for the immediate relief of anginal symptoms (Class I, Level C) (2). Nitroglycerin is initially given sublingually. If a patient's angina persists, an intravenous (IV) nitroglycerin infusion may be utilized. Side effects include hypotension and headache. A significant contraindication to the administration of nitrates is the concurrent use of sildenafil (Viagra®). According to the ACC/AHA recommendations, nitrates should not be given within 24 hours of sildenafil use, as this combination may result in prolonged vasodilation, profound hypotension, and death (Class III, Level A) (2).

Morphine sulfate. Morphine sulfate is commonly used in UA/NSTEMI for its potent analgesic and anxiolytic properties. Morphine also has potentially beneficial hemodynamic effects, including venodilation and modest decreases in heart rate and systolic blood pressure. However, no randomized trials have established the unique impact of morphine on myocardial ischemia or patient prognosis.

The ACC/AHA guidelines suggest that intravenous morphine sulfate may be given when a patient's anginal pain is not immediately relieved with nitroglycerin or when acute pulmonary congestion or severe anxiety is present (Class I, Level C) (2). Potential adverse effects of morphine include hypotension, nausea, vomiting, and respiratory depression.

Beta-blockers. Beta-blockers decrease myocardial oxygen demand and cardiac work by lowering heart rate and contractility. The resulting increase in the duration of diastole also increases the time available for coronary perfusion. These drugs act by competitively inhibiting the action of circulating catecholamines on cell membrane beta-adrenergic receptors.

The evidence supporting the efficacy of beta-blocker administration in UA is somewhat limited. The supposed benefit of beta-blockers in the treatment of UA is largely based on extrapolation from quality randomized studies involving other ischemic forms of CAD, such as STEMI, stable angina, and heart failure. Trials of beta-blocker use in all these subgroups of patients have shown a reduction in mortality and morbidity (50, 51). On the other hand, there is only limited randomized trial data specifically addressing the morbidity and mortality associated with beta-blocker use for UA patients. An overview of smaller studies concluded that beta-blockers were beneficial in reducing the risk of progression of UA to MI by 13% (52). However, these trials lacked sufficient power to effectively assess the impact of beta-blockers on mortality rates for UA. Several small studies of UA patients have also shown that beta-blockers are effective in reducing the frequency and duration of anginal episodes (53–56).

The ACC/AHA guidelines recommend that beta-blockers be started early in UA/NSTEMI in the absence of contraindications (Class I, Level B) (2). Contraindications include bradycardia, hypotension, acute congestive heart failure, and heart block (first degree block greater than 240 ms or any form of 2nd or 3rd degree block). Reactive airway disease is considered a relative contraindication. If necessary, patients with a history of bronchospasm may be given a beta-1 selective agent with a shorter half-life and then observed closely for adverse effects. All high-risk ACS patients, as well as those with ongoing chest pain, should be given an initial loading dose intravenously, followed by oral administration. Oral agents may be selected for lower-risk patients. Dosing should be tailored to achieve a target resting heart rate of 50–60 beats per minute.

Calcium-channel blockers. Calcium-channel blockers decrease the influx of calcium ions across cardiac and smooth muscle cell membranes. These agents may be classified into two groups: dihydropyridine calcium-channel antagonists (e.g., nifedipine and amlodipine) and non-dihydropyridine calcium-channel antagonists (e.g., verapamil and diltiazem). The dihydropyridines exert prominent effects on peripheral vascular smooth muscle relaxation. In contrast, verapamil and diltiazem have more potent cardiac effects, including depression of myocardial contractility, heart rate, and atrioventricular (AV) node conduction. All of these agents have similar coronary vessel dilation properties. Potential adverse effects include hypotension, congestive heart failure, bradycardia, and AV block.

The use of calcium-channel blockers in UA/NSTEMI has been fairly well researched, with the majority of data focused upon nifedipine use. Nifedipine and other rapid release, short-acting dihydropyridines have been clearly shown to cause harm in the setting of UA/NSTEMI by causing a rapid drop in blood pressure and a reflex activation of the sympathetic nervous system. As these agents have been shown to increase adverse outcomes in the setting of ACS, the ACC/AHA guidelines strongly recommend that immediate-release dihydropyridine calcium antagonists should not be given (Class III, Level A) unless a beta-blocker is administered concurrently (Class IIb, Level B) (2, 56–58).

The potential risks and benefits of verapamil and diltiazem in UA/NSTEMI have also been studied. Several controlled trials have shown no harmful effects associated with the non-dihydropyridines when they are given early to patients with ACS, and they have suggested a strong trend toward a beneficial reduction in mortality and morbidity (59–61). However, much of the strongest evidence is limited to symptom control, with several randomized trials demonstrating that non-dihydropyridine calcium-channel blockers relieve or prevent ischemic symptoms to a degree similar to that of beta-blockers (62, 63).

Therefore, based on the available evidence, the ACC/AHA guidelines recommend the alternative administration of a non-hydropyridine calcium antagonist to patients with persistent or frequently recurring ischemia if a beta-blocker is contraindicated and severe left ventricular dysfunction is absent (Class I, Level B). An oral, long-acting calcium-channel blocker may also be considered for recurrent ischemia refractory to beta-blockers and nitrates (Class IIa, Level C) (2).

ACE inhibitors. ACE inhibitors have been shown in several large-scale randomized trials to decrease morbidity and mortality for ACS patients. The greatest benefit seems to be found among patients with left ventricular (LV) dysfunction in the setting of an acute or recent MI (64–66) and/or diabetes (67). A recent trial also demonstrated a significant reduction in mortality and other adverse outcomes for high-risk CAD patients with normal LV function treated with an ACE inhibitor (68). Therefore, according to the ACC/AHA guidelines, an ACE inhibitor should be started in ACS patients with LV dysfunction and/or diabetes, especially when hypertension persists despite treatment with nitrates and beta-blockers (Class I, Level B). An ACE inhibitor may also be considered for all post-ACS patients (Class IIa, Level B) (2). These agents should generally be started within 24 hours of admission.

Anti-platelet Therapy

Anti-platelet agents decrease coronary thrombus formation and propagation by inhibiting various key components of platelet activation and aggregation.

Aspirin. Aspirin (ASA) decreases platelet activation and aggregation by irreversibly inhibiting platelet cyclooxygenase-1, which in turn reduces production of thromboxane A2. Strong evidence supports the efficacy and safety of aspirin in patients with ACS (69–73). A meta-analysis of four randomized trials comparing ASA with placebo in UA/NSTEMI showed a 49% relative risk reduction in the endpoint of death or MI in patients receiving ASA therapy (from 12.5% to 6.4%) (2). UA studies have also demonstrated the long-term protective effect of ASA, which may persist for at least 1–2 years.

Therefore, for all patients with a suspected or confirmed diagnosis of ACS and no contraindications, the ACC/AHA guidelines recommend that aspirin should be given as soon as possible after patient presentation and continued indefinitely for those with CAD (Class I, Level A) (74). Contraindications to ASA include allergy, active bleeding, intolerance, severe untreated hypertension, and active peptic ulcer disease. Patients who are unable to take ASA should alternatively be given clopidogrel (refer to clopidogrel discussion below). An overview of trials evaluating ASA use by patients with CAD found similar efficacy of the drug at daily doses ranging from 75–325 mg per day (69). However, no study has directly compared the efficacy of varying ASA doses in UA/NSTEMI patients. The ACC/AHA guidelines recommend an initial ASA dose of 160–325 mg of a non-enteric-coated formulation, which may be chewed to rapidly achieve a therapeutic blood level (2).

ADP receptor antagonists. Clopidogrel (Plavix®) and ticlopidine (Ticlid®) are thienopyridines that noncompetitively antagonize the platelet adenosine diphosphate (ADP) receptor and therefore exert inhibitory effects on platelet activation and aggregation. Unlike ASA, which has a prompt onset of action, clopidogrel and ticlopidine have a more delayed pharmacokinetic profile, and it may take several days for these drugs to achieve their full anti-platelet effects without a loading dose. Clopidogrel is preferred over ticlopidine because it has a more rapid onset of action and a more favorable safety profile (75, 76). The adverse effects of ticlopidine, which include potentially life-threatening hematologic disorders, have limited this drug's clinical usefulness.

Clopidogrel has been shown to have comparable efficacy and safety to that of ASA in the secondary prevention of adverse cardiovascular events in patients with atherosclerotic vascular disease (77). Therefore, as an alternative, the ACC/AHA guidelines recommend that clopidogrel should be administered to hospitalized patients with UA/NSTEMI who are unable to take ASA because of an allergy or other contraindication (Class I, Level A) (74).

One of the major changes to the ACC/AHA guidelines has been the inclusion of a Class I recommendation for the routine use of clopidogrel in addition to ASA in the management of patients with UA/NSTEMI (74). This update was based on the findings of two recent large clinical trials. The CURE trial demonstrated for the first time the incremental benefit of adding clopidogrel to aspirin therapy (78). CURE randomized 12,562 patients with UA/NSTEMI (within 24 hours of symptom onset) to receive clopidogrel or placebo in addition to ASA for 3–12 months. Approximately 72% of patients in both treatment arms were also receiving unfractionated heparin (UFH) or LMWH at the time of randomization. At twelve months follow-up, the composite primary outcome of cardiovascular death, MI, or stroke occurred in 9.3% of patients in the clopidogrel group and 11.4% in the placebo group (RR 0.80, $p<0.001$). Patients who received clopidogrel also had significantly lower rates of in-hospital refractory ischemia and revascularization. Some of the beneficial effects of clopidogrel were seen within 4 hours of drug administration. There was a 33% relative risk reduction in the primary end point plus refractory ischemia in the clopidogrel group compared to placebo within 24 hours of randomization. The incremental benefit of clopidogrel combined with ASA was also observed across all TIMI risk score groups (79). Since CURE was conducted at centers without a routine policy of early invasive procedures, revascularization was only performed in 23% of patients. The beneficial effects of clopidogrel were partially offset by a small but significant increase in major bleeding in the clopidogrel group (3.7%) compared to the placebo group (2.7%) (RR 1.38, $p=0.001$). This risk of major bleeding was disproportionately higher for patients undergoing CABG within the first 5 days of clopidogrel discontinuation (78).

The PCI-CURE trial evaluated the combination of clopidogrel and ASA for UA/NSTEMI patients undergoing PCI. A total of 2,658 patients were randomized to treatment with clopidogrel or placebo. Patients were then pretreated with the study drug plus ASA for a median of 10 days overall. The median time to PCI was 6 days. After PCI was performed, most patients received either clopidogrel or ticlopidine for four weeks, followed by the initial study drug for a mean of eight months. Patients in the clopidogrel group experienced significantly fewer adverse cardiovascular outcomes (death, MI, or need for urgent revascularization) within 30 days of PCI as well as longer term (80).

As a result of the data from CURE and PCI-CURE, the 2002 ACC/AHA guideline update recommends the administration of clopidogrel in addition to ASA to hospitalized patients with UA/NSTEMI who are managed either with an early interventional or medical approach and are not at high risk for bleeding. Clopidogrel should be given for at least 1 month (Class I, Level A) and may be continued for up to 9 months (Class I, Level B) (74). When clopidogrel is given with ASA, a lower dose of ASA (75–100 mg per day) is suggested, as recent data have shown no additional benefit but increased bleeding complications associated with higher doses of ASA (81).

It should also be noted that the specific optimal timing of clopidogrel administration is not exactly clear from the data or the guidelines. Due to the increased risk of perioperative bleeding, the ACC/AHA guidelines suggest that clopidogrel should be withheld for 5–7 days before CABG (Class I, Level B) (74). Since the incidence of CABG in clinical trials ranges from 11–17% in patients with UA/NSTEMI (82), one proposed strategy is to withhold clopidogrel from patients expected to receive coronary catheterization within 24– 36 hours of admission. Once the coronary anatomy is known and it is clear that CABG will not be required in the near-term, a loading dose of clopidogrel may be given in the catheterization lab prior to PCI if necessary (2, 83). To better define the specific timing of drug administration, additional data on the bleeding risks and benefits of clopidogrel use in patients managed interventionally needs to be collected in future studies (82, 84, 85).

Glycoprotein IIb/IIIa inhibitors. Activation of the integrin GP IIb/IIIa receptor found on platelets is the final common pathway to platelet aggregation, leading to the binding of circulating molecules such as fibrinogen to these receptors and the cross linking of adjacent platelets. Several agents have been developed which antagonize the GP IIb/IIIa receptor. Three drugs are currently available for intravenous administration in the US: abciximab (Reopro®), tirofiban (Aggrastat®), and eptifibatide (Integrilin®). Several large, randomized trials have shown that oral GP IIb/IIIa inhibitors do not have a documented benefit and are associated with increased mortality in the setting of unstable ACS (86–88); therefore, only the intravenous agents will be discussed in the following sections.

In recent years, there has been extensive research on the safety and efficacy of GP IIb/IIIa inhibitors in the management of UA/NSTEMI. Initial trials were focused on those patients undergoing PCI (elective or urgent), in the hopes that procedure-related thrombotic complications could be minimized (32, 89–94). Many of the patients enrolled in these studies had UA or NSTEMI. Overall, these PCI trials have demonstrated the efficacy of GP IIb/IIIa inhibition in conjunction with PCI in reducing the rate of adverse events. Recent studies have looked at the potential expanded application of GP IIb/IIIa inhibitors in the primary medical treatment of UA/NSTEMI patients (95–98) and will be discussed in more detail in the following sections.

Abciximab. Abciximab is a Fab (fragment antigen binding) fragment of a monoclonal antibody and acts as a noncompetitive inhibitor of the GP IIb/IIIa receptor. Abciximab has a long half-life, with platelet activity returning to normal within 48 hours after an infusion is stopped.

The CAPTURE trial evaluated treatment with abciximab prior to percutaneous intervention. The study recruited 1,265 patients with refractory UA and a proven culprit lesion on angiogram amenable to PTCA. These patients were randomized to either placebo or an infusion of abciximab for 18–24 hours prior to and 1 hour after PTCA. All patients concurrently received ASA and UFH. Abciximab significantly reduced the relative risk of the 30-day composite endpoint (death, MI, or need for urgent revascularization) by 29%. Major bleeding was infrequent but occurred more often with abciximab compared with placebo (3% vs. 2%). However, a *post hoc* subgroup analysis found that the benefits of abciximab in this study were limited only to those patients with an elevated troponin T at the time of study entry (92).

The GUSTO IV-ACS trial studied the use of abciximab by 7,800 UA/NSTEMI patients who were not anticipated to undergo early (less than 48 hours) invasive revascularization. Patients were randomized to receive placebo or an abciximab infusion for 24 or 48 hours. All patients were given ASA and heparin (LMWH or UFH). The composite endpoint was death or MI at 30 days. This trial showed a trend toward no benefit from treatment with abciximab, although the results were not statistically significant. This lack of benefit was consistently observed in most subgroups including higher risk patients with an elevated troponin (98). Therefore, based on this data, the 2002 ACC/AHA guideline update does not recommend abciximab administration for patients in whom PCI is not planned (Class III, Level A) (74).

Tirofiban. Tirofiban is a synthetic non-peptide that competitively inhibits the GP IIb/IIIa receptor. Due to its reversible binding of the GP IIb/IIIa receptor, tirofiban has a short half-life with a return of normal platelet activity within 3–4 hours after discontinuation of the drug.

The PRISM study compared a 48-hour treatment period with either tirofiban or UFH in combination with ASA for 3,232 patients with UA/NSTEMI. Sixty-two percent of the patients underwent angiography. Nearly 40% had subsequent percutaneous revascularization, but only 1.9% of the patients had this procedure performed during the first 48 hours. The composite outcome of death, MI, or refractory ischemia at 48 hours was significantly reduced by 32% in the tirofiban group, although this benefit was not maintained at 30 days. There was, however, an improved 30-day mortality with tirofiban. No significant differences in bleeding complications were observed between the two groups. The PRISM trial showed that tirofiban, as compared with heparin, reduced the incidence of ischemic events during the 48-hour treatment period prior to the performance of revascularization procedures (95). In a subgroup analysis, tirofiban was noted to significantly decrease the 30-day risk of death or MI, but this treatment benefit was only seen in patients with a positive troponin level regardless of whether they were managed medically or invasively (31).

In the PRISM-PLUS trial, 1,915 patients with UA/NSTEMI were randomized to receive tirofiban, UFH, or tirofiban plus UFH for a mean duration of 71 hours. All patients were also given ASA. Compared with the PRISM study, patients enrolled in PRISM-PLUS were higher risk, with 90% undergoing angiography and 54% receiving revascularization after 48 hours. The tirofiban alone treatment arm was terminated early due to excess mortality at 7 days. The composite primary endpoint of death, MI, or refractory ischemia at 7 days was lower for patients who received tirofiban plus UFH compared with those who received UFH alone. This treatment benefit was maintained at 30 days and 6 months. The combination of tirofiban and UFH was also associated with a reduction in the frequency of death or MI at 7 days, 30 days, and 6 months. The benefits were consistent in different subgroups of patients, including those treated medically or interventionally. No significant differences in major bleeding were noted (96).

The RESTORE trial enrolled 2,139 patients undergoing coronary interventions within 72 hours of presentation with an ACS and randomized them to receive either tirofiban or placebo. All patients were already receiving ASA and heparin prior to randomization. In the tirofiban group, there was a significant 38% relative reduction in the composite end point of death, MI, or reintervention noted at 2 days after angioplasty and a 27% decrease at 7 days. Thirty days after intervention, the decline in adverse events was not statistically significant (32).

Eptifibatide. Eptifibatide is a synthetic peptide that competitively inhibits the GP IIb/IIIa receptor. It has a pharmacokinetic profile similar to that of tirofiban, with a short half-life and a return of normal platelet activity within 3 to 4 hours after discontinuation of the drug.

The PURSUIT trial randomized 10,948 patients with UA/NSTEMI to treatment with either placebo or eptifibatide for up to 72 hours. All patients received standard therapy with ASA and UFH. Relative to the placebo group, the incidence of the primary composite endpoint of death or MI at 30 days was reduced in the eptifibatide group from 15.7% to 14.2% (RR 0.91, p=0.042). The benefits were seen as early as 96 hours and persisted at 6-month follow-up. Subgroup analysis showed that the greatest benefit associated with eptifibatide was observed in those patients who underwent PCI. There was also a lack of efficacy in women compared to men. Bleeding was more common in the eptifibatide arm, but there was no increase in the incidence of hemorrhagic stroke (97).

Early administration of GP IIb/IIIa inhibitors. The early administration of GP IIb/IIIa inhibitors in UA/NSTEMI has been addressed both in the context of medical management and interventional strategies, although no prospective randomized clinical trial has directly evaluated this issue. Indirect post-randomization analyses of data from the CAPTURE, PRISM-PLUS, and PURSUIT trials have shown a statistically significant reduction in the incidence of death or MI during the period of early medical management with a GP IIb/IIIa inhibitor in each study (99). These three trials combined demonstrated a 34% relative reduction in death or MI during the period of study drug infusion before a possible intervention. PCI was performed in almost all CAPTURE patients, in 30.5% of PRISM-PLUS patients, and in 13.0% of PURSUIT patients. A greater benefit was seen in those patients who actually underwent PCI, with a decrease in the event rate during the first 48 hours after PCI.

An observational study of 60,770 NSTEMI patients in the National Registry of Myocardial Infarction-4 (NRMI-4) database analyzed in-hospital outcomes associated with the early use of GP IIb/IIIa inhibitors in a community-based population (100). NSTEMI patients treated with a GP IIb/IIIa inhibitor within 24 hours after presentation had significantly lower odds for in-hospital mortality compared with untreated patients (adjusted OR 0.88, 95% CI 0.79-0.97). Similar survival benefits associated with early GP IIb/IIIa inhibitor therapy were also seen in the subgroup of patients who did not receive PCI or cardiac catheterization.

A meta-analysis conducted by Boersma et al. included six large randomized GP IIb/IIIa inhibitor trials (including GUSTO IV-ACS) involving 31,402 patients with UA/NSTEMI who were not routinely scheduled to undergo early coronary revascularization (101). At 30 days after randomization, a significant but small reduction in the odds of death or MI in the GP IIb/IIIa treatment group compared with placebo or control was observed (10.8% vs. 11.8%, OR=0.91, 95% CI 0.84 to 0.98, p=0.015). The absolute treatment benefit was greatest for high-risk patients. However, decreases in the individual endpoints of death or nonfatal MI did not achieve statistical significance. In this meta-analysis, 11,965 (38%) of the 31,402 patients actually underwent PCI or CABG within 30 days, despite not being routinely scheduled for early intervention. Within this subgroup, patients treated with GP IIb/IIIa inhibitors experienced a significant decrease in the odds of death or MI (OR 0.89, 95% CI 0.80 to 0.98). On the other hand, no significant difference in efficacy was seen in the 19,416 patients who did not receive coronary revascularization with PCI or CABG (OR 0.95, CI 0.86 to 1.05, p=NS). In terms of safety, major bleeding complications were significantly more common with GP IIb/IIIa inhibitors (2.4% vs. 1.4%, p<0.0001), but the incidence of intracranial bleeding was not significantly different.

Roffi et al. performed a meta-analysis including the same six ACS trials analyzed by Boersma et al.; however, they excluded 1,832 patients (the no-heparin arm in PRISM-PLUS and the low-dose eptifibatide arm in PURSUIT) (102). Twenty-one percent of the patients in this meta-analysis underwent PCI. Based on the composite endpoint of death or MI at 30 days, the beneficial treatment effect of GP IIb/IIIa inhibitors was small and statistically insignificant for patients medically managed (OR 0.95, p=0.27) but was significantly greater for those who underwent PCI (OR 0.82, p=0.01). Among patients who received PCI, the benefit was more pronounced if revascularization was performed during GP IIb/IIIa inhibitor infusion instead of after study drug discontinuation.

The TIMI risk score has also been tested as a clinical tool used to help identify UA/NSTEMI patients who might benefit from early medical treatment with GP IIb/IIIa inhibitors. In the PRISM-PLUS trial, 1,069 patients did not undergo early PCI, and tirofiban appeared to be beneficial only for a high-risk subgroup of these patients with TIMI risk scores greater than or equal to 4. This benefit was seen whether patients later received PCI or not (40). Additionally, several trials, including CAPTURE and PRISM, have demonstrated an enhanced efficacy of GP IIb/IIIa inhibitors in the treatment of higher risk UA/NSTEMI patients with a positive troponin level at the time of presentation (29–31).

Summary of GP IIb/IIIa inhibitors. Based on the available evidence, GP IIb/IIIa inhibitors are of substantial benefit for patients with UA/NSTEMI who receive PCI. These drugs are of only modest benefit for patients who are not initially scheduled to undergo early PCI but eventually do have the procedure performed. They are of questionable benefit for patients who are medically managed without intervention, but may be selectively useful in the conservative treatment of high-risk patients.

The ACC/AHA 2002 guidelines (74) strongly recommend the administration of a GP IIb/IIIa inhibitor, in addition to ASA and heparin, to UA/NSTEMI patients for whom catheterization and PCI are planned (Class I, Level A). A GP IIb/IIIa inhibitor may also be given to patients already receiving triple therapy with ASA, heparin, and clopidogrel if PCI is planned (Class IIa, Level B). The data supporting quadruple anti-thrombotic therapy is limited, with no clinical trials to date directly studying the potential incremental benefits of adding a GP IIb/IIIa inhibitor to a regimen of ASA, heparin, and clopidogrel. Eptifibatide or tirofiban may be indicated in the medical treatment of UA/NSTEMI patients with high-risk features, including an elevated troponin or refractory ischemia, and may be given in addition to ASA and LMWH or UFH (Class IIa, Level A). Medical therapy with eptifibatide or tirofiban for patients without high-risk features is not supported by strong data and is therefore only a Class IIb, Level A ACC/AHA recommendation. Abciximab should not be administered to patients for whom PCI is not planned (Class III, Level A).

The evidence supporting the efficacy of early therapy with GP IIb/IIIa inhibitors prior to invasive treatment of UA/NSTEMI is limited. Therefore, the ACC/AHA 2002 guideline update provides no specific guidance on the optimal timing of GP IIb/IIIa inhibitor administration and states that these drugs may be given just prior to PCI (e.g., in the catheterization laboratory) (74).

Thrombolysis

Several studies have demonstrated the failure of thrombolytics in improving outcomes for UA/NSTEMI patients and have instead shown an increase in the risk of MI and bleeding (103–106). Therefore, the ACC/AHA guidelines recommend that intravenous fibrinolytic therapy should not be given to patients unless they have indications such as acute ST-segment elevation, new or presumed new left bundle-branch block, or a true posterior MI (Class III, Level A) (74).

Anti-thrombotic Therapy

Anti-thrombotic agents prevent thrombus propagation via inhibitory effects on thrombin activity as well as on components of the coagulation cascade. UFH and LMWH indirectly block thrombin through the cofactor antithrombin. Several anticoagulants (e.g., hirudin, bivaluridine) directly inhibit thrombin, but these drugs are mainly experimental or in limited use and will not be discussed in this article.

Unfractionated heparin (UFH). UFH is a glycosaminoglycan composed of heterogeneous chains with varying molecular weights and anticoagulation activity. The anticoagulant effect of heparin is primarily mediated by its interaction with antithrombin III. Heparin accelerates the ability of antithrombin III to inactivate the coagulation enzymes, factor IIa (thrombin), factor Xa, and factor IXa. UFH also has significant pharmacokinetic limitations that are mainly due to its nonspecific binding to plasma proteins and cells. These limitations result in wide variation of anticoagulant response in individual patients. Due to this unpredictability in clinical effect, monitoring of activity with activated partial thromboplastin time (aPTT) is required. A weight-adjusted IV bolus of UFH followed by continuous infusion is recommended. Subsequent dosing should be adjusted based on a laboratory-specific nomogram with an aPTT goal of 1.5–2.5 times control (107).

UFH is widely used in the management of patients with UA/NSTEMI and is considered part of the standard of care. Several clinical trials have shown that the early administration of UFH either alone or in combination with ASA is associated with a decreased risk of MI or ischemia (70, 73, 108, 109). Most of these studies, however, were too underpowered to define any mortality benefits. In a meta-analysis of randomized trials comparing the combined use of UFH and ASA with ASA alone, the rate of death or MI during the first week of therapy was reduced by 53% ($p=0.018$) (2). Composite data from another meta-analysis also demonstrated an incremental benefit of UFH with ASA; however, the findings did not reach statistical significance (110).

Therefore, for the management of UA/NSTEMI, the ACC/AHA guidelines recommend anticoagulation with either UFH or LMWH in addition to anti-platelet therapy with ASA and/or clopidogrel (Class I, Level A) (74).

Low-molecular-weight heparin (LMWH). LMWHs are derived by cleavage of UFH to yield smaller chains with different molecular weights and anticoagulant activity. Compared with UFH, LMWHs are relatively more potent in catalyzing the inhibition of factor Xa by antithrombin III than in the inactivation of thrombin. Due to their reduced binding to proteins or cells, LMWHs have a more predictable dose-response relationship and a longer half-life than UFH. As a result, the advantages of LMWHs include no general requirement for laboratory monitoring of activity and more convenient subcutaneous administration once or twice a day (107). Two LMWH agents are currently approved in the US for the treatment of UA/NSTEMI: enoxaparin and dalteparin.

In recent years, there have been several large clinical trials evaluating the efficacy and safety of LMWH in the management of patients with UA/NSTEMI. Early studies focused on comparing LMWH with placebo. For example, the FRISC trial demonstrated a significant superiority of the LMWH dalteparin over placebo in aspirin-treated patients with UA and non-Q-wave MI (111).

Most of the subsequent clinical research has centered on directly comparing an LMWH with UFH in the treatment of UA/NSTEMI. The FRIC study demonstrated a trend toward equivalence between dalteparin and UFH (112).

The first two large clinical trials to compare enoxaparin and UFH in the management of UA/NSTEMI were published in the late 1990s. They provided strong data that enoxaparin was superior in efficacy compared to UFH. The ESSENCE trial randomized 3,171 patients with UA/NSTEMI to treatment with either enoxaparin or UFH in addition to ASA for 2–8 days. The composite outcome of death, MI, or recurrent angina was significantly decreased at 14- and 30-day follow-up in patients receiving enoxaparin (39). The TIMI 11B study demonstrated a similar superiority of enoxaparin over UFH (38). At one-year follow-up, the benefits of enoxaparin persisted in both study groups (113). A meta-analysis of data from the ESSENCE and TIMI 11B trials reported a 20% reduction in death and serious cardiac ischemic events seen within the first few days of treatment through 43 days (114). These studies also proved the safety of enoxaparin, with no excessive increase in major hemorrhage but a small increase in minor bleeding noted.

Both the ESSENCE and TIMI 11B trials were conducted in an era when conservative management strategies predominated in the treatment of UA/NSTEMI. If a planned percutaneous or surgical intervention was performed, enoxaparin was discontinued 6 to 12 hours before and replaced with UFH. The use of newer anti-platelet medication classes such as the thienopyridines and GP IIb/IIIa antagonists were also significantly limited during this time period. Over the last few years, however, there has been an evolving trend towards a more aggressive management approach with earlier invasive therapies and more frequent administration of drugs such as clopidogrel and GP IIb/IIIa inhibitors. As a result, subsequent comparative trials evaluating the efficacy and safety of enoxaparin in relation to UFH have focused on the drug's application in the setting of aggressive management strategies.

Several studies have established the safety of enoxaparin given prior to PCI. Collet et al., in a study of 293 patients with UA/NSTEMI, showed that PCI could be performed safely and effectively within 8 hours of the last enoxaparin dose (115). In an observational study of the NICE registry (NICE-1), intravenous enoxaparin was given to 828 patients undergoing elective PCI (116). The rate of major and minor bleeding was also comparable to that of historical controls given UFH. Patients in both of these trials underwent PCI without GP IIb/IIIa blockade.

Growing evidence has also accumulated showing that LMWH can be used safely and efficaciously in combination with a GP IIb/IIIa inhibitor, particularly in the setting of PCI (116-121). These trials have demonstrated either improved efficacy or safety of LMWH or noninferiority of LMWH in comparison with UFH. Almost all of these trials studied the use of enoxaparin. The recently completed SYNERGY trial enrolled 10,027 high-risk patients with UA/NSTEMI who were managed with an intended early invasive strategy. These patients were randomized to receive either enoxaparin or UFH prior to angiography. All patients received ASA or clopidogrel if a contraindication to ASA was present. Other agents were given as recommended per ACC/AHA guidelines, with close to 60% of patients in both enoxaparin and UFH groups receiving a GP IIb/IIIa inhibitor. The overall study results showed that enoxaparin was not superior to but was at least as effective as UFH. Major bleeding was slightly more frequent with enoxaparin; however, there was no statistically significant difference in the number of patients receiving transfusions. The study concluded that enoxaparin is a safe and effective alternative to UFH for the treatment of high-risk patients likely to undergo an early invasive procedure (122). A systematic overview of six randomized controlled trials comparing enoxaparin and UFH in the treatment of UA/NSTEMI has also been recently published (123). This review of approximately 22,000 patients, with varying degrees of risk and concomitant treatment strategies, noted a significant reduction in the combined end point of death or MI at 30 days with enoxaparin versus UFH (10.1% vs 11.0%, OR 0.91) and no significant differences in major bleeding or blood transfusions.

In summary, enoxaparin and dalteparin have been shown to be at least as effective as UFH in the treatment of UA/NSTEMI, with a similar rate of major bleeding. LMWH can be used in place of UFH, especially in light of its practical advantages. LWMH may also be given safely prior to PCI without the need to transition to UFH as well as in the presence of a GP IIb/IIIa inhibitor. However, LMWH should not be given if CABG surgery is planned within 24 hours. Numerous studies have shown enoxaparin to have a superior efficacy compared to UFH. In general, the ACC/AHA guidelines suggest that enoxaparin may be preferable to UFH in the treatment of patients with UA/NSTEMI (Class IIa, Level A) (74).

The Role of Early Invasive Revascularization

There has been much controversy and ongoing research dedicated to examining the effects on clinical outcomes associated with an early invasive versus an early conservative management strategy in UA/NSTEMI. In an early conservative strategy, aggressive medical treatment is first initiated. Coronary angiography and any necessary revascularization procedures are reserved only for patients who later develop recurring evidence of ischemia despite maximal medical therapy, or who manifest other high-risk clinical or non-invasive test findings. In an early invasive strategy, patients withou contraindications undergo early planned coronary catheterization and intervention with PCI or CABG as indicated. Within the invasive approach, two alternative protocols have evolved. One option is to proceed immediately to angiography. In contrast, planned catheterization may be deferred for 12–48 hours or more after a period of medical stabilization or "cooling off" (124, 125).

Three older randomized trials demonstrated similar outcomes with early conservative and invasive treatment strategies (103, 126, 127). The TIMI IIIb trial, conducted in the early 1990s, randomized 1,473 UA/NSTEMI patients to an early invasive or early conservative strategy. At six weeks, the composite endpoint of death, MI, or a strongly positive stress test occurred for 16.2% of the early invasive patients compared with 18.1% of the early conservative group (p=0.33). Similarly, the incidence of death or MI showed no significant difference between treatment strategies (103).

The VANQWISH trial randomized 920 patients within 72 hours of the onset of a non-Q-wave MI to either early invasive or conservative management. The number of patients with the primary endpoint of death or non-fatal MI at hospital discharge was significantly higher in the early invasive group (36 vs. 15 patients, p=0.004). This increased risk of death or MI in the early invasive group persisted at one month and at one year. A statistically significant increase in mortality was also seen in the early invasive arm at hospital discharge, at one month, and at one year. This study concluded that most patients with non-Q-wave MI do not benefit from routine, early invasive management and that a conservative, ischemia-guided approach was safer and more effective. However, there were several limitations to this trial. The excess mortality observed in the invasive group was primarily accounted for by the much higher 30-day mortality rates of patients randomized to surgical revascularization with CABG compared to PCI and conservative treatment (7.7% vs. 1.3% and 1% respectively). Additionally, this study was conducted during a period when newer and more effective therapies such as GP IIb/IIIa inhibitors and coronary stents were in limited clinical use (126).

The MATE study enrolled 201 ACS patients who were ineligible for thrombolytic treatment and randomized them to an early invasive or conservative strategy. Death and reinfarction occurred at similar rates for both groups, and no long-term benefit in cardiac outcomes was seen at 21-month follow-up (127).

In contrast to earlier studies, more recent trials have showed a benefit from early invasive management compared with early conservative treatment. In the FRISC II trial, 2,457 patients from multiple Scandinavian centers were randomly assigned to a routine invasive or non-invasive strategy after an initial medical treatment period averaging 6 days with ASA, nitrates, beta-blockers, and dalteparin. After six months, death or MI occurred in 9.4% of the invasive group compared to 12.1% of the non-invasive group (RR 0.78, p=0.031). The results were independent of the randomized dalteparin treatment. It should be noted, however, that in this European study the planned invasive approach was intentionally delayed after a prolonged course of medical pretreatment, and this sequence may be difficult to adopt in US centers (124). Moreover, other studies have shown that deferral of intervention for a prolonged medical pre-treatment period has not improved outcomes compared with earlier intervention (125, 128).

The TACTICS-TIMI 18 trial randomized 2,220 UA/NSTEMI patients to either an early invasive strategy with coronary angiography performed within 48 hours followed by revascularization as needed, or to a conservative medical strategy. All patients received ASA, heparin, and tirofiban. At six months, the composite endpoint of death, MI, or rehospitalization for ACS was significantly reduced in the invasive group compared to the medically managed group (15.9% vs. 19.4%, p=0.025). The incidence of death or MI was also significantly lower in the invasive arm at six months. In a subgroup analysis, the beneficial effects observed in the early invasive group were only present in patients with higher risk features, defined in this study as troponin elevation, ST-segment deviation, or a TIMI risk score greater than 3. In terms of safety, the rates of major bleeding were similar in both the invasive and non-invasive groups (34).

Therefore, current evidence suggests that routine therapy of UA/NSTEMI with an early invasive approach is associated with better outcomes compared with an early conservative medical strategy, particularly in high-risk patients. Caution must be exercised in comparing older trials with more modern studies employing different overall treatment methods. For instance, the use of GP IIb/IIIa inhibitors was low or non-existent in earlier trials. In contrast, patients in the TACTICS-TIMI 18 trial received a GP IIb/IIIa inhibitor for an average of 22 hours prior to coronary angiography. This adjunctive upstream use of a GP IIb/IIIa inhibitor may have lessened the hazards formerly associated with PCI in early invasive groups. The more widespread use of advanced coronary stenting instead of balloon angioplasty may have also

Pearls and Pitfalls

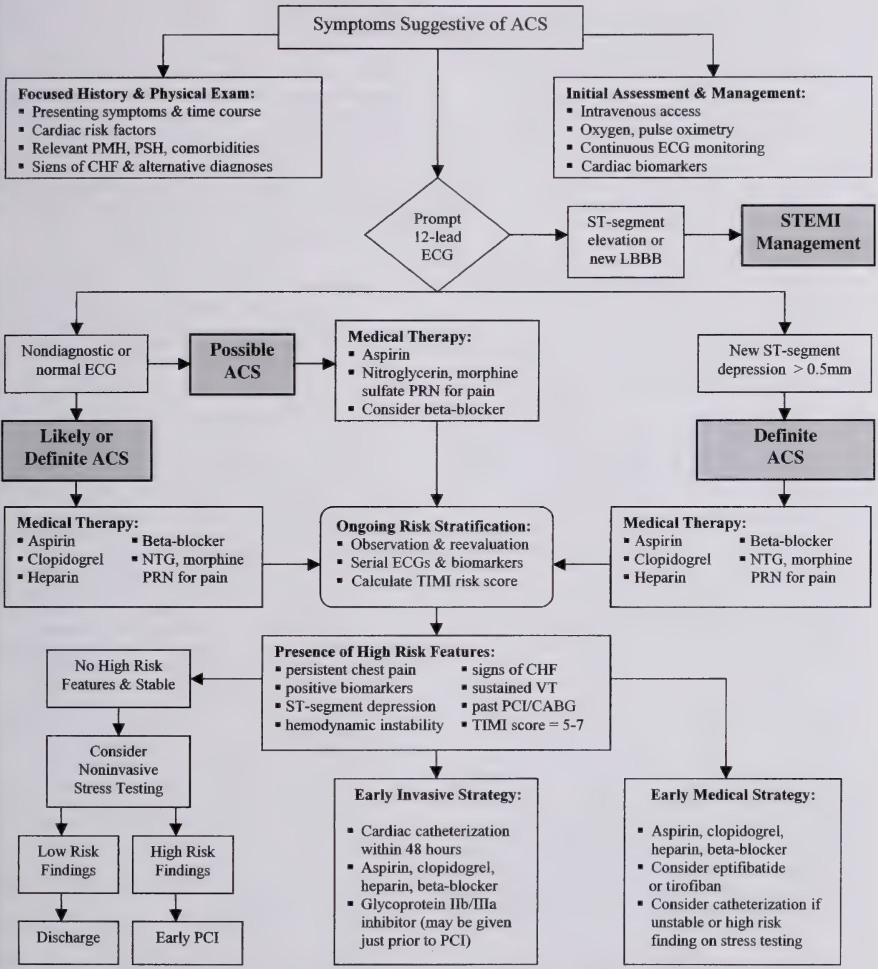
Intervention	Advantages	Disadvantages
Obtain an ECG early for all patients with suspected ACS	quick, readily available screening test	a normal or nondiagnostic ECG does NOT exclude a cardiac etiology
The TIMI risk score may be used as a risk stratification tool	simple and practical; may be used to tailor therapies	need to wait for results of cardiac enzymes; should be used in conjunction with clinical judgment
Aspirin should be given early to ALL suspected ACS patients without a contraindication	highly effective; inexpensive; readily available	small risk of bleeding
Consider low-molecular-weight instead of unfractionated heparin	enoxaparin may be more effective, especially in high-risk patients; simple dosing; easier subcutaneous administration; no requirement for laboratory monitoring; lower incidence of heparin-induced thrombocytopenia	more frequent minor, but not major, bleeding; expensive; limited, but growing experience with glycoprotein IIb/IIIa inhibitors and PCI; unfractionated heparin is recommended during CABG
Glycoprotein IIb/IIIa inhibitors should be selectively given to patients undergoing PCI or at high risk	proven benefit in the setting of PCI	expensive; increased bleeding risk
Abciximab should NOT be given to patients medically managed		may worsen outcomes if no PCI is planned; irreversible, long half-life
Thrombolytics should NOT be given to patients with UA/NSTEMI		no proven efficacy in UA/NSTEMI; may worsen outcomes
High-risk patients should be considered for an early invasive strategy	increasing data to support the benefits of PCI in high-risk patients	limited availability; expensive

ACS=acute coronary syndrome; CABG=coronary artery bypass graft; ECG=electrocardiogram; NSTEMI=non-ST-elevation myocardial infarction; PCI= percutaneous coronary intervention; UA=unstable angina

played a beneficial role in improved clinical outcomes with an early invasive strategy. A recent meta-analysis of five modern trials conducted in the era of GP IIb/IIIa inhibitors and intra-coronary stents reported improved survival associated with routine invasive therapy (129). A total of 6,766 UA/NSTEMI patients were randomized to either routine invasive versus conservative treatment. Compared with medical management, an invasive strategy demonstrated a reduction in the composite endpoint of death or MI at 30 days (RR 0.61, 95% CI 0.45 to 0.84), at 6 months (RR 0.75, 95% CI 0.63 to 0.89), and at 12 months (RR 0.78, 95% CI 0.65 to 0.92). Mortality in the invasive group

FIGURE

Evidence-Based Evaluation and Management of Acute Coronary Syndromes


Symptoms Suggestive of ACS
Focused History & Physical Exam:
Presenting symptoms & time course
Cardiac risk factors
Relevant PMH, PSH, comorbidities
Signs of CHF & alternative diagnoses
Initial Assessment & Management:
Intravenous access
Oxygen, pulse oximetry
Continuous ECG monitoring
Cardiac biomarkers
Prompt 12-lead ECG
ST-segment elevation or new LBBB
STEMI Management
Nondiagnostic or normal ECG
Possible ACS
Medical Therapy:
Aspirin
Nitroglycerin, morphine sulfate PRN for pain
Consider beta-blocker
New ST-segment depression > 0.5mm
Likely or Definite ACS
Definite ACS
Medical Therapy:
Aspirin
Clopidogrel
Heparin
Beta-blocker
NTG, morphine PRN for pain
Ongoing Risk Stratification:
Observation & reevaluation
Serial ECGs & biomarkers
Calculate TIMI risk score
Medical Therapy:
Aspirin
Clopidogrel
Heparin
Beta-blocker
NTG, morphine PRN for pain
No High Risk Features & Stable
Presence of High Risk Features:
persistent chest pain
positive biomarkers
ST-segment depression
hemodynamic instability
signs of CHF
sustained VT
past PCI/CABG
TIMI score = 5-7
Consider Noninvasive Stress Testing
Low Risk Findings
High Risk Findings
Discharge
Early PCI
Early Invasive Strategy:
Cardiac catheterization within 48 hours
Aspirin, clopidogrel, heparin, beta-blocker
Glycoprotein IIb/IIIa inhibitor (may be given just prior to PCI)
Early Medical Strategy:
Aspirin, clopidogrel, heparin, beta-blocker
Consider eptifibatide or tirofiban
Consider catheterization if unstable or high risk finding on stress testing

ACS=acute coronary syndrome; CABG=coronary artery bypass graft; CHF=congestive heart failure; ECG=electrocardiogram; LBBB=left bundle branch block; NTG=nitroglycerin; PCI=percutaneous coronary intervention; PMH=past medical history; PRN=as needed; PSH=past surgical history; STEMI=ST-segment-elevation myocardial infarction; VT=ventricular tachycardia

was also decreased at 6–12 months (RR 0.80, 95% CI 0.63 to 1.03) and at 24 months (RR 0.77, 95% CI 0.60 to 0.99). Men and troponin-positive patients had significant reductions in the rates of death or MI. However, the reduction in relative risk of death or MI for women and troponin-negative patients was equivocal and statistically insignificant. Recent advances in the development of drug-eluting intracoronary stents may further improve outcomes for patients with UA/

TABLE 2
Key Concepts

- The history, physical exam, electrocardiogram, and cardiac biomarkers are collectively used to formulate both the diagnosis of UA/NSTEMI and the overall assessment of patient prognosis and risk.
- Risk stratification of patients with UA/NSTEMI is used to tailor the intensity and aggressiveness of therapies to the subset of patients most likely to benefit.
- All patients with a suspected or confirmed diagnosis of UA/NSTEMI should be given aspirin as soon as possible after presentation unless a contraindication exists.
- Clopidogrel should be administered in addition to aspirin to patients hospitalized with UA/NSTEMI. However, clopidogrel should be withheld for 5 to 7 days prior to CABG.
- Higher risk patients incrementally benefit the most from treatment with low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, and early invasive procedures.
- UA/NSTEMI patients may safely be anti-coagulated with a low-molecular-weight heparin instead of unfractionated heparin even in the setting of a planned PCI and/or in the presence of a glycoprotein IIb/IIIa inhibitor.
- A glycoprotein IIb/IIIa inhibitor should be administered to UA/NSTEMI patients for whom cardiac catheterization and PCI are planned and may be given in addition to aspirin, heparin, and/or clopidogrel.

CABG = coronary artery bypass graft; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; UA = unstable angina

NSTEMI undergoing an early invasive approach (130, 131).

Therefore, based on the available evidence, the 2002 ACC/AHA guidelines for UA/NSTEMI recommend an early invasive strategy for patients with any high-risk indicators and no contraindications to angiography or revascularization (Class I, Level A). In the absence of these high-risk features, either an early conservative or invasive strategy for hospitalized patients is suggested (Class I, Level B) (74).

Conclusions

There is now a multitude of therapeutic options available to the clinician caring for patients presenting with UA and NSTEMI. Key concepts in the evaluation and treatment of UA/NSTEMI are listed in Table 2. An overview of the evidence-based evaluation and management of acute coronary syndromes is presented in the Figure. There is strong clinical evidence in the literature supporting the risk stratification of patients with potential UA/NSTEMI and the tailoring of specific therapies to the risk profile of the patient. Early, timely diagnosis and management of these patients are critical, as growing evidence demonstrates improved patient outcomes with early aggressive treatment, particularly in higher risk groups. It is important that clinicians become familiar with the existing recommended practice guidelines related to the management of UA/NSTEMI. More favorable patient outcomes have been seen when clinical implementation of evidence-based guidelines is performed (132–135). As new clinical data emerge, clinicians will be challenged with incorporating these additional findings into their clinical practices.

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Diagnosis and Management of ST Elevation Myocardial Infarction:

A Review of the Recent Literature and Practice Guidelines

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Abstract

There is a large volume of literature available to guide the peri-infarct management of ST elevation myocardial infarction (STEMI). Most of this literature focuses on improving the availability and efficacy of reperfusion therapy. The purpose of this article is to review contemporary scientific evidence and guideline recommendations regarding the diagnosis and therapy of STEMI.

Studies and epidemiological data were identified using Medline, the Cochrane Database, and an Internet search engine. Medline was searched for landmark and recent publications using the following key words: STEMI, guidelines, epidemiology, reperfusion, fibrinolytics, percutaneous coronary intervention (PCI), facilitated PCI, transfer, delay, clopidogrel, glycoprotein IIb/IIIa, low-molecular-weight heparin (LMWH), beta-blockers, nitrates, and angiotensin-converting enzyme (ACE) inhibitors.

The data accessed indicate that urgent reperfusion with either fibrinolytics or percutaneous intervention should be considered for every patient having symptoms of myocardial infarction with ST segment elevation or a bundle branch block. The utility of combined mechanical and pharmacological reperfusion is currently under investigation. Ancillary treatments may utilize clopidogrel, glycoprotein IIb/IIIa inhibitors, or low molecular weight heparin, depending on the primary reperfusion strategy used. Comprehensive clinical practice guidelines incorporate much of the available contemporary evidence, and are important resources for the evidence-based management of STEMI.

Key Words: Diagnosis, fibrinolysis, myocardial infarction, PCI, reperfusion, review, STEMI, therapy, treatment.

Introduction

WITH THE DEVELOPMENT of reperfusion strategies and ancillary therapies over the past three decades, the prognosis of ST elevation myocardial infarction (STEMI) has improved significantly. There is a large body of literature addressing the optimal management of these patients in the acute setting, much of which has been incorporated into recent clinical practice guidelines (1–4). In fact, data available from the National Registry of Myocardial Infarction (NRMI) has revealed a steady increase between 1990 and 1999 in the percentage of practitioners who adhere to the published guidelines (5). This evidence-based approach may have helped to reduce the in-hospital mortality among patients with STEMI to the current level of approximately 9.5% (5). The purpose of this article is to review current evidence and recommendations for the evaluation and early treatment of STEMI.

Epidemiology

Acute myocardial infarction (AMI) remains a public health problem of epidemic proportions. Recent data from the American Heart Association (AHA) reveal a prevalence of myocardial infarction (MI) of 1.9–5.2%, which varies by age, sex, and ethnicity (6). In the United States annually, there are 565,000 first-time, and 300,000 recurrent, myocardial infarctions (6). Interestingly, in the last decade the NRMI registries have recorded a decrease in the percentage of patients with myocardial infarction who present with ST segment elevation (from 36% to 27%, $p \leq< 0.001$), while the percentage presenting without ST segment elevation has increased (from 45% to 63%, $p \leq< 0.001$) (5). But rather than representing a true change in the incidence of disease, this may be due to the growing use of troponin assays, which have increased overall diagnostic sensitivity for myocardial infarction.

Diagnosis

Symptomatology

Although the formal diagnosis of AMI requires documentation of elevated cardiac biomarkers (7), time delays in biomarker elevation limit their usefulness in early decision making. For this reason,

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Glossary

ACC = American College of Cardiology
ACCP = American College of Chest Physicians
ACE = angiotensin-converting enzyme
ACEP = American College of Emergency Physicians
ACS = acute coronary syndrome
AHA = American Heart Association
AMI = acute MI
aPTT = activated partial thromboplastin time
ASA = aspirin
BBB = bundle branch block
CABG = coronary artery bypass graft
ECG = electrocardiogram
ED = emergency department
ESC = European Society of Cardiology
GP IIb/IIIa = glycoprotein IIb/IIIa
GRACE = Global Registry of Acute Coronary Events
ICH = intracranial hemorrhage
IRA = infarct-related artery
LBBB = left BBB
LMWH = low-molecular-weight heparin
MI = myocardial infarction
MIR = Myocardial Infarction Registry
MITRA = Maximal Individual Therapy in AMI
NRMI = National Registry of Myocardial Infarction
PCI = percutaneous coronary intervention
RBBB = right BBB
RCT = randomized controlled trial
RV = right ventricular
STEMI = ST elevation myocardial infarction
TIMI = thrombosis in myocardial infarction
t-PA = tissue plasminogen activator
UFH = unfractionated heparin

initial diagnostic and treatment decisions rely primarily on clinical features and electrocardiogram (ECG) findings. Time of symptom onset is important, as it affects management options. Symptom onset within 12 hours is the generally accepted window of eligibility for fibrinolytic therapy (1). Despite an absence of data demonstrating a mortality benefit after this 12-hour window (8), guidelines state that fibrinolytics should also be administered to patients presenting between 12 and 24 hours if they have persistent symptoms and ST segment elevation (1). The therapeutic window is similar for primary percutaneous coronary intervention (PCI), with eligibility extending to 12–24 hours after symptom onset if ischemic symptoms are persistent(1).

Ischemic symptoms are often described as "typical" (with chest pain) or "atypical" (without chest pain) (Table 1, [9]). Recently, the multinational Global Registry of Acute Coronary Events (GRACE) found that of 20,881 patients with acute coronary syndrome (ACS), 1,763 (8.4%) presented without chest pain; of those patients without chest pain, the most common atypical chief complaint was dyspnea (9). Although it is frequently assumed that a typical presentation is more commonly associated with ECG changes, in fact, patients with both typical and atypical symptoms are equally likely to have ischemic changes on the index ECG (9). Of concern, delayed diagnosis for patients with atypical symptoms appears common. In the GRACE registry, this group received an admitting diagnosis other than ACS 24% of the time (vs. 2.4% of the typical presenters). Presumably as a result, patients with atypical presentations were significantly less likely to receive fibrinolysis (25.6% vs. 45.6%, $p < 0.001$), primary PCI (11.0% vs. 21.0%, $p < 0.001$), or ancillary therapy such as aspirin (ASA) or beta-blockers. Not surprisingly, many of the risk factors associated with an atypical presentation (Table 2, [10]) have also been identified as risk factors for delayed reperfusion (11, 12).

TABLE 1
Most Common "Atypical" Chief Complaints with Myocardial Infarction (9)

Dyspnea	(49%)
Diaphoresis	(26%)
Nausea or vomiting	(24%)
Pre-syncope or syncope	(19%)

Electrocardiographic Diagnosis

The ECG is the primary diagnostic tool used to identify an STEMI, and is of central importance because it identifies those patients who are candi-

TABLE 2
Risk Factors for Presentation with and without Chest Pain (10)

With Chest Pain	Without Chest Pain
Tobacco use	Older age
Hypercholesterolemia	Diabetes
Prior PCI or CABG	Prior heart failure
	Nonwhite race
	Female sex

PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft.

dates for emergent reperfusion therapy. The definition of ST elevation "indicative of myocardial ischemia," as proposed by the Joint Committee of the European Society of Cardiology (ESC) and American College of Cardiology (ACC) for the redefinition of MI, is a new, or presumed new, ST segment elevation in 2 or more contiguous leads of at least 2 mm at the J point in leads V1–V3, or 1 mm in other leads (7). It should be noted that, historically, inclusion criteria for reperfusion trials have varied in the amount of ST elevation required to diagnose a myocardial infarct. In the 2004 guidelines for management of STEMI, the ACC and AHA recommend that patients with symptoms of AMI and ST segment elevation of 1 mm in any 2 contiguous leads be considered for reperfusion therapy (1). In their discussion, the ACC and AHA acknowledge that using a 2 mm cut-off would increase the specificity of diagnosis of anteroseptal MI in the setting of early repolarization. Recognizing this diagnostic ambiguity, the American College of Emergency Physicians (ACEP) provided more detailed ECG criteria for emergent fibrinolytic therapy: ST segment elevation greater than 1 mm in 2 or more contiguous leads that are not characteristic of early repolarization or pericarditis, nor of a repolarization abnormality from left ventricular hypertrophy or bundle branch block (BBB) (4).

Decision-making is more complicated when a BBB confounds ECG interpretation. The ACC and AHA recommend reperfusion therapy for patients with "new or presumably new" left bundle branch block (LBBB) (1), and the American College of Chest Physicians (ACCP) recommends treatment for "LBBB of unknown duration" (3). However, several trials and the large meta-analysis of fibrinolytic therapy by the FTT Collaborative Group found a significant mortality benefit for patients presenting with any BBB, not just new LBBB (8, 13, 14). ACEP therefore recommends considering emergent reperfusion therapy for patients with clinical presentation suggestive of AMI and with a right, left, paced, atypical, new, or old BBB (4).

Reperfusing any patient with suggestive symptoms and a BBB, while an option, is a strategy favoring diagnostic sensitivity over specificity. For this reason, attempts have been made to improve diagnostic accuracy in the setting of a conduction delay. A right bundle branch block (RBBB) generally confounds the ECG interpretation of an acute infarct less than does an LBBB; findings of myocardial infarction are usually evident with RBBB because electrocardiographic signs of early activation of the left ventricle are not altered (15). In contrast, identification of myocardial ischemia in the presence of LBBB is quite difficult. Numerous criteria exist for the diagnosis of AMI in this setting, of which the most widely accepted are those developed by Sgarbossa (Table 3, [16]). When used in combination, these criteria were initially reported to have a sensitivity of 36% and specificity of 96%. Performance characteristics in follow-up studies have been somewhat variable, and inter-observer agreement on the ECG interpretation has ranged from excellent to fair (17, 18).

Two additional points should be kept in mind when evaluating an ECG for evidence of possible AMI. First, ST segment depression in the anteroseptal precordial leads may actually represent posterior ST segment "elevation." In fact, the occurrence of maximal ST segment depression in leads V2 and V3 is 70% sensitive and 96% specific for an occlusive lesion of the left circumflex artery (19), and should be investigated further with acquisition of posterior lead tracings to rule out a posterior STEMI. While fibrinolytic therapy is considered an "option" for a true posterior STEMI (4), the preferred reperfusion modality is PCI (1). Second, patients with inferior STEMI should be screened for right ventricular (RV) infarction by looking for ST segment elevation in the right precordial lead V4R. Approximately 10–15 % of patients with a RV infarction will have clinically significant hemodynamic abnormalities, and this subgroup is at high risk for a poor outcome (1).

Reperfusion Therapy

Options for Reperfusion Therapy

Reperfusion of the infarct-related artery (IRA) is the cornerstone of therapy for STEMI. Fibrinolysis and percutaneous coronary intervention (PCI) are both well established as effective options, but PCI has generally come to be regarded as the treatment of choice. A recent meta-analysis of 23 randomized, controlled trials (RCTs) comparing PCI to fibrinolysis revealed that PCI reduced short-term mortality (7% vs. 9%, p=0.0002), non-fatal re-infarction (3% vs. 7%, $p < 0.0001$), and stroke (1% vs. 2%, p=0.0004) when compared to fibrinolysis (20). Mortality and re-infarction benefits

TABLE 3

Sgarbossa Criteria for Identifying Acute Myocardial Infarction in Left Bundle Branch Block (16)

ST elevation ≥ 1 mm in leads with dominant R waves
ST elevation ≥ 5 mm in leads with dominant S waves
ST depression ≥ 1 mm in V1, V2 or V3

of PCI in this analysis were maintained through long-term follow-up, and were still significant when trials using the older fibrinolytic streptokinase, and patients with cardiogenic shock were excluded. Despite these results, the issue is still a matter of some debate in the literature, and as noted in the ACC/AHA guidelines, it is not possible to say that one modality is superior for all patients in all settings. There is also concern that outcomes achieved with PCI in the setting of clinical trials may not be reproducible in the "real world," mainly because RCTs usually enroll a select group of patients who are cared for by experts in high-volume centers. Registry data corroborate this argument: Analysis from the NRMI registry, which included hospitals of various sizes with a wide geographic distribution in the US, revealed that while PCI provided a greater mortality benefit than fibrinolysis in centers with an intermediate or high volume of procedures per year, there was no mortality benefit in low volume centers (fewer than 17 procedures per year) (21). Furthermore, registries consistently reveal significantly longer delays between presentation and invasive treatment than reported in RCTs. For example, the NRMI-2 registry found a median door-to-balloon time of 116 minutes (11). This finding is of concern because door-to-balloon times of over 120 minutes have been correlated with worse outcomes (11), and the current ACC/AHA recommended door-to-balloon time is less than 90 minutes (1).

Trends in Reperfusion Therapy

Despite the above considerations, PCI is becoming more widely available, and trends in reperfusion therapy reflect an increasing preference for PCI. For example, among patients who presented to hospitals in the US capable of performing coronary artery bypass graft (CABG), the use of fibrinolytic therapy fell from 59.1% in 1994 to 47.9% in 1999, whereas the use of primary PCI increased from 11.8% to 24.4% (both p=0.0001) (5). Pooled data from two German registries, the Maximal Individual Therapy in AMI (MITRA) study and Myocardial Infarction Registry (MIR), which also looked at reperfusion trends between 1994 to 1998, found that the proportion of patients receiving PCI increased from 6.3% to 19% (22). Of note, the percentage of patients with STEMI or LBBB presenting within 12 hours of symptom onset who received emergent reperfusion therapy increased only slightly in the US (from 68.8% to 70.0%, p=0.0014) during this same time period. This suggests that invasive therapy is being preferentially employed mainly for fibrinolytic-eligible candidates, rather than as a means of reperfusing fibrinolytic-ineligible patients (5).

Expanding Access to Reperfusion Therapy

There are impediments to the delivery of both pharmacologic and mechanical reperfusion, including ambiguous clinical presentation, perceived risks of therapy, or lack of access to PCI. Fibrinolytic therapy is used less frequently for certain groups of patients. A retrospective European chart review published in 1996 revealed that 37% of fibrinolytic-eligible patients without contraindications did not receive treatment, and regression analysis identified age and female gender as independent risk factors for treatment being withheld (23). A recent systematic review of studies investigating the role of race in health care found that ethnic minorities were also less likely to receive fibrinolysis, even independent of economic status (24). These studies document, but do not explain, these disparities.

While age, female gender, and race are also associated with a likelihood of not receiving invasive reperfusion (24, 25), the major barrier remains a lack of access to 24-hour interventional catheterization laboratories. One strategy used to expand access to PCI involves transfer of patients from community hospitals to PCI-capable referral centers. This idea was first prospectively investigated in a small feasibility study which found a low incidence of complications during transport (26). Several subsequent randomized controlled trials have also evaluated this approach, the largest of which was DANAMI-2, with more than 1,500 patients (27). Although this study demonstrated that transfer for primary PCI was significantly better than treatment with t-PA in reducing the combined primary endpoint of death, re-infarction, or disabling stroke at 30 days (8.5% vs. 14.5%, p=0.002), several points must be addressed before routine implementation of this strategy can be recommended. First, the only component of the combined outcome which achieved statistical significance was a reduction in the rate of re-infarction, yet a majority of patients who failed fibrinolysis or had recurrent ischemia with ST segment elevation were treated with repeat fibrinolysis rather than rescue PCI, even though the latter is the preferred therapy (1, 2). Second, the inter-hospital transfer system was highly organized, with a median presentation-to-transfer delay of only 50 minutes, and a median actual transfer time of 32 minutes, a degree of efficiency that would be difficult to replicate outside of a trial, or in a different geographic setting. Nevertheless, a subsequent meta-analysis of the five major studies of transfer for PCI, enrolling a total of 2,466 patients, found a significant reduction in mortality with transfer (relative risk 0.69, 95% CI 0.51 to 0.92, p=0.01) (28). If these trial conditions can be approximated, transfer for primary PCI appears to be a reasonable option. However, as recent data from the NRMI-4 have noted an average door-to-balloon time for transferred patients of 185 minutes (29), it would appear that considerable improvement is needed before this becomes routine practice.

Rather than centralizing care at referral centers, another option is to increase the availability of PCI at community hospitals. The C-PORT trial, which took place in eleven community hospitals without pre-existing invasive capabilities or cardiovascular surgery back-up, found that after the establishment of PCI programs through a formalized, comprehensive development process, PCI was superior to fibrinolysis in reducing re-infarction (5.3% vs. 10.6%, p=0.04) and hospital length of stay (4.5 vs. 6.0 days; p=0.02). However, no mortality benefit was demonstrated at 6 weeks or 6 months (30). While this data is encouraging, procedural volume is strongly correlated to patient outcomes, a concern if the number of PCI programs at low volume hospitals increases.

Pharmacologic Reperfusion

Due to its universal availability, fibrinolysis remains the mainstay of reperfusion therapy. The development of newer, fibrin-specific fibrinolytics, such as t-PA, reteplase, and tenecteplase, represents a small but significant improvement over the first-generation drugs (i.e., streptokinase and urokinase). The newer agents have the advantage of activating plasminogen to form the clot-lysing enzyme plasmin when they are bound to fibrin in a thrombus, thereby promoting targeted fibrinolysis rather than systemic anticoagulation, and theoretically improving clot lysis while lowering the risk of bleeding. The GUSTO-1 mega-trial, a comparison of streptokinase versus t-PA, confirmed that the accelerated t-PA regimen with unfractionated heparin (UFH) reduces 30-day mortality in comparison with streptokinase plus UFH (6.3% vs. 7.4%, p=0.001), with this benefit persisting at one year (31).

Although more efficacious than with older agents, reperfusion following administration of newer, fibrin-specific fibrinolytics still remains imperfect, with 90 minute "patency" rates (thrombosis in myocardial infarction [TIMI] grade 2 or 3 flow) of 75 to 80% (32–34). Reteplase and tenecteplase, recombinant and genetically engineered derivatives of tissue plasminogen activator (t-PA), offer greater ease of administration via bolus dosing; however, neither has demonstrated a survival benefit (35, 36).

Risks of Reperfusion Therapy

The benefits of fibrinolytic therapy must be weighed against the risks, the most serious of which is stroke. Analysis of GUSTO-I found that 1.4% of the 41,021 subjects suffered an adverse cerebrovascular event. Hemorrhagic and non-hemorrhagic strokes were most common in the t-PA arm (0.70% and 0.66%, respectively), less common in the streptokinase plus intravenous UFH arm (0.57% and 0.64%), and least common in the streptokinase plus subcutaneous UFH arm (0.46% and 0.56%) (37). The excess of strokes due to t-PA did not negate the overall benefit: a combined end point of death or disabling stroke was significantly lower in the t-PA group than in the streptokinase groups (6.9% vs. 7.8%, p=0.006) (31). Because of an increased risk of intracranial bleeding, the ACC and AHA consider any history of intracranial hemorrhage, or ischemic stroke within the past 3 months (but not within the past 3 hours), as an absolute contraindication to fibrinolysis (1).

Bleeding is the other major risk of fibrinolytic therapy. Severe bleeding, causing substantial hemodynamic compromise requiring intervention or treatment, occurred in 1.2% of patients in the GUSTO-I trial (38). It was most commonly procedure-related (associated with coronary artery bypass surgery or PCI), and was more common with streptokinase plus intravenous UFH than with the other fibrinolytic and heparin combinations (38). Of the newest fibrinolytic agents, tenecteplase therapy was found to be complicated by fewer major bleeds and blood transfusions than t-PA (4.66% vs. 5.94%, p=0.0002; 4.25% vs. 5.49%, p=0.0002, respectively) (36).

Prehospital Fibrinolysis

The benefit of fibrinolysis is greatest when administered early following the onset of symptoms, and declines rapidly after the first several hours (8, 39). In select settings, prehospital fibrinolysis appears to offer a mortality advantage over in-hospital administration. A meta-analysis of 6 trials with 6,434 patients found a reduction in all-cause hospital mortality (odds ratio 0.83, 95% CI 0.70–0.98) with prehospital fibrinolysis (40). All studies included in this meta-analysis enrolled only patients presenting within 4–6 hours of symptom onset, a critical factor considering that the time saved by prehospital administration (approximately 60 minutes) is probably most beneficial during the early hours of an infarction. The prehospital strategy would seem particularly well suited to rural regions or hospitals with large catchment areas. In a recent prospective, observational cohort study in Scotland, it was indeed shown that "rural" patients who lived further than 10 miles from the study hospital and received prehospital fibrinolysis had the shortest call-to-needle times (median of 52 minutes). This compared favorably with either patients living within 10 miles receiving in-hospital fibrinolysis (median 80 minutes) or the rural patients receiving in-hospital treatment (median 125 minutes) (41). The most recent North American study, ER-TIMI, had a primary outcome measure of time to administration of fibrinolytics, and confirmed a reduction in time to treatment of 32 minutes, from a median of 63 ($p < 0.0001$) (42). Possibly limiting their external validity, a majority of the above trials administered the drug in a mobile intensive care unit with an intensivist on the scene.

Combined Pharmacological and Mechanical Reperfusion

In an important modification of the usual prehospital strategy, the CAPTIM study group combined prehospital fibrinolysis with transfer to an invasive center for rescue PCI, if needed, and compared this with primary PCI (43). As a result of this approach, 26% in the fibrinolysis group received early angioplasty. Overall, there was no significant difference in the primary composite endpoint of death, non-fatal reinfarction, and non-fatal disabling stroke at 30 days between the two groups, although there was a trend towards benefit in the primary PCI group, with a composite endpoint of 6.2% vs. 8.2% (risk difference 1.96, 95% CI 1.53–5.46). When interpreting these results, one should understand that with only 840 patients, this study was probably underpowered to detect a significant difference.

The role of a combined pharmacological and mechanical approach has been a topic of much discussion, i.e., whether the use of PCI should be driven by evidence of ischemia, or routinely employed. PCI after primary fibrinolysis is clearly indicated for patients who develop cardiogenic shock or pulmonary edema, and is also recommended by the ACC and AHA, albeit with less supporting evidence, for patients with hemodynamic or electrical instability, and/or persistent symptoms (in this case called "rescue PCI") (1). A more disputed regimen is so-called "facilitated PCI," which includes full or partial dose fibrinolytics, alone, or in combination with glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, started prior to early, planned PCI. This strategy is appealing because it combines the immediate availability of fibrinolytics with the higher patency and lower reinfarction rates of PCI, and would seem particularly well suited to patients being transferred from a community hospital to an interventional center.

Most early trials comparing primary PCI with full-dose fibrinolytics prior to immediate PCI found an increase in bleeding and other complications without demonstrating a reduction in adverse cardiovascular events (44, 45). The idea has been revisited, however, with newer pharmacologic agents and interventional techniques. Recent investigative efforts have concentrated on facilitating PCI with a combination of reduced-dose fibrinolytics and GP IIb/IIIa inhibitors (e.g., abciximab). SPEED, a small pilot trial which primarily investigated 60–90 minute angiographic patency rates after abciximab, with or without reteplase, also provided a *post hoc* assessment of facilitated PCI, as 61% of 528 patients received an intervention at the time of angiography (46). While conclusions were limited by the lack of randomization between those who did and did not receive PCI, there was a significantly lower rate of reinfarction and urgent revascularization at 30 days in the facilitated group. Another study, BRAVE, compared two different pharmacologic strategies prior to PCI: abciximab versus abciximab plus half-dose reteplase. Initial TIMI grade 3 flow was more common in the combination arm, and TIMI grade 0 flow more common in the abciximab alone arm. Procedural success was, however, the same, and there was no difference in the primary endpoint of infarct size as measured by SPECT (47). Unfortunately, there was no control group of primary PCI or medical therapy, and therefore the efficacy of facilitated PCI *per se* could not be determined. Upcoming trials include ASSENT-4, ADVANCE MI, and FINESSE, all of which will further assess facilitated PCI with various fibrinolytic and GP IIb/IIIa regimens. The ACC and AHA provide a class IIb recommendation, based on this "conflicting evidence," that facilitated PCI may be performed as a reperfusion strategy in higher-risk patients when PCI is not immediately available and bleeding risk is low (1).

Another reperfusion strategy is early PCI, where routine PCI is employed hours to days after fibrinolysis, rather than as soon as possible, as is the case with facilitated PCI. Early PCI would reduce the need for expensive 24-hour catheterization laboratories, and lessen the demand for resource consumption by the emergency department (ED), or catheterization laboratory transfer. Although an attractive strategy, the literature regarding its efficacy remains inconclusive. A routine invasive strategy after fibrinolysis (i.e. not symptom driven) was given a class IIb recommendation by the ACC and AHA in the most recent edition of their guidelines. This is in contrast to a class I recommendation for PCI after fibrinolysis in the setting of recurrent MI, provocable ischemia or shock, and weaker than the class IIa recommendation for patients with CHF, an ejection fraction < 40%, or serious arrhythmias (1). Subsequent to the publication of these guidelines, the GRACIA trial was completed; it randomized 500 patients who received accelerated t-PA for STEMI to either routine angiography between 6 and 24 hours after fibrinolysis (with intervention if indicated) or ischemia-driven PCI (48). Patients received guideline-recommended adjunctive therapy (e.g., ASA, beta-blockers, stenting, etc.) as appropriate. Before hospital discharge, 21% (52 of 251) of patients in the ischemia-driven group needed cardiac catheterization for either spontaneous ischemia with ECG changes or stress-induced ischemia. At one year, the primary combined endpoint of death, reinfarction, or ischemia-induced revascularization was significantly less common in the routine angiography group (9% vs. 21%, p=0.0008), although the results were largely driven by a reduction in revascularization. Readmission due to ischemia by one year was also reduced from 25% to 15% (p=0.006) in the routine angiography group. Limitations of this study include an open design, relatively small sample size, lack of a primary PCI control group, and the inclusion of ischemia-induced revascularization in the combined endpoint (as this was, by definition, part of the treatment strategy for the ischemia-driven group). Nonetheless, this interesting study found no increase in complications and a trend towards reduction in death and reinfarction (49).

Patient Characteristics and Choice of Reperfusion Strategy

There may be utility in "triaging" fibrinolytic-ineligible and high risk patients with evidence of congestive heart failure to emergent PCI, as these are two groups of patients for whom primary PCI is clearly the recommended primary therapy (1). In the absence of these factors, if presentation is within 3 hours of symptom onset, the ACC/AHA guidelines state no preference for either strategy (1). This recommendation is based on emerging evidence that fibrinolysis is as effective as PCI for patients presenting early. In a subgroup analysis of the PRAGUE-2 trial comparing treatment with streptokinase at a community hospital with transfer for primary PCI, patients randomized within 3 hours of symptom onset had similar 30-day mortality, whereas those presenting later had significant benefit from transfer and an invasive approach (mortality 6.0% vs. 15.3%, p<0.02) (50). A subgroup analysis was also performed on data from the above-mentioned CAPTIM trial, which revealed a trend towards benefit of prehospital fibrinolysis over PCI for patients randomized within 2 hours (2.2% vs. 5.7%, p=0.058) (51). Registry data support these observations as well: in a retrospective analysis of the MIR/MITRA data, the adjusted mortality was no different for treatment with fibrinolytics and PCI when the prehospital delay was less than 3 hours; however, for patients presenting later, PCI was preferred (52).

Adjunctive Therapies

Reperfusion therapy, while central to the treatment of STEMI, must be accompanied by appropriate adjunctive treatments. PCI actually promotes thrombus formation through iatrogenic vessel injury and stent placement, and platelets may become hyperactive approximately 24 hours after intervention (53). Thus, one of the major early complications of PCI is acute and subacute vessel closure. Anti-platelet agents have proven themselves to be valuable adjuncts to mechanical reperfusion by reducing these early thrombotic complications. Adjunctive therapy is also important following administration of fibrinolytics—it is thought that fibrin-specific agents, while promoting local clot lysis, may actually exert a systemic pro-coagulant effect through increased thrombin activity (54) and possibly via enhanced platelet aggregation (55). Myocardial protective agents, particularly beta-blockers, complement reperfusion therapy. Additionally, the impact of specialized cardiac care units on improved patient outcomes should be acknowledged; some authors consider this to be one of the most important innovations in the care of the patient with STEMI in recent decades (53).

Anti-platelet Therapy

Aspirin plays a critical role in the suppression of platelet function by inhibiting formation of the platelet activator, thromboxane A2. It should be given as early as possible to any patient without a true contraindication for the treatment of STEMI, whether in combination with fibrinolysis or PCI

(1). Its benefit was clearly demonstrated in the ISIS 2 trial, which compared ASA and streptokinase, alone and in combination, in 17,187 patients (56). Aspirin mono-therapy resulted in a significant reduction in five-week vascular mortality from 11.8 to 9.4% ($p<0.00001$). Additionally, aspirin significantly reduced non-fatal reinfarction (1.0% vs. 2.0%) and non-fatal stroke (0.3% vs. 0.6%) compared with placebo, and was not associated with an increase in intracranial hemorrhage or bleeds requiring transfusion.

Clopidogrel and ticlopidine both cause platelet inhibition via adenosine diphosphate-receptor antagonism, but clopidogrel is preferred to ticlopidine due to a lower risk of serious side effects. There is little outcome data on the benefit of clopidogrel in combination with fibrinolytics. Clopidogrel is recommended, based largely on consensus, for patients receiving fibrinolysis who cannot tolerate aspirin due to allergy (1, 3). For patients undergoing PCI with stenting, combination therapy with ASA and clopidogrel is standard for the reduction of adverse cardiovascular events, including occlusive stent thrombosis. However, these recommendations are largely based on data from trials of patients undergoing elective PCI or PCI for non-STEMI acute coronary syndromes (1). Because clopidogrel should be withheld for 5 – 7 days prior to CABG, the administration of clopidogrel should generally be delayed until angiography has been performed and the preferred treatment plan (PCI or CABG) has been determined.

Glycoprotein IIb/IIIa inhibitors interfere with the final common pathway in platelet aggregation, namely the cross linking of platelets by fibrinogen. Their utility in reducing recurrent ischemia or infarction after PCI for acute coronary syndromes has been well demonstrated (57). The rationale for the use of GP IIb/IIIa inhibitors in STEMI is similar, but there is considerably less data on this group of patients. The largest and strongest study to date, CADILLAC, enrolled 2,082 stent-eligible patients with STEMI or LBBB to angioplasty alone, angioplasty with abciximab, stenting, or stenting plus abciximab (58). At six months, the composite endpoint of death, reinfarction, stroke, and ischemia-driven revascularization of the IRA had occurred in 20.0% of patients after angioplasty, 16.5% after angioplasty plus abciximab, 11.5% after stenting, and 10.2% after stenting plus abciximab ($p<0.001$).

The other studies investigating the efficacy of GP IIb/IIIa inhibitors in STEMI also showed a similar, small reduction in urgent ischemia-induced revascularization (59, 60). The ADMIRAL trial was of particular interest because, while a significant overall reduction in the combined, 30-day and 6-month endpoints of death, re-infarction, or urgent revascularization was seen, this benefit was only realized in patients who received abciximab in the prehospital setting or in ED (60). The benefit of early administration was further evaluated in a meta-analysis of six randomized trials of early (before transfer to the catheterization laboratory) versus late (at the time of PCI) administration of abciximab or tirofiban in patients with STEMI (61). There was a trend towards mortality benefit (3.4 vs. 4.7%) with early rather than late administration at the longest follow-up period for each study. Thus, with the caveat that their recommendation is based on a relatively small number of patients who received abciximab and PCI for STEMI across several trials, the ACC and AHA suggest that it is reasonable to start abciximab as early as possible prior to primary PCI, with or without stenting, for STEMI (1). The ACCP similarly recommends abciximab for patients undergoing PCI, stating that it should be started prior to balloon inflation when possible (57).

GP IIb/IIIa inhibitors have also been studied as a supplement to full and reduced-dose fibrinolytics, although reduced dosing is now preferred due to concerns about excess risk of bleeding with full dosing. The largest trial to date with clinical outcome measures, GUSTO V, randomized over 16,000 patients in 20 countries to reteplase, or abciximab with half-dose reteplase (62). There was no difference in the primary endpoint of 30-day mortality, although there was a significant reduction in reinfarction and recurrent ischemia in the combined group. While an increase in intracranial hemorrhage (ICH) was not noted with combination therapy, there was a significant increase in other severe bleeding complications compared with reteplase alone. ASSENT 3, the other large trial (6,095 patients) investigating combination therapy, sought to evaluate the role of the low-molecular-weight heparin (LMWH) enoxaparin (see below) as well, comparing (a) full-dose tenecteplase and enoxaparin, (b) half-dose tenecteplase with low-dose heparin and abciximab, against the control regimen of (c) full-dose tenecteplase with weight-adjusted UFH (63). The primary efficacy endpoint, including death, in-hospital reinfarction, or refractory ischemia at 30 days, was lower in groups (a) and (b) than in controls (group [c]) (11.4%, 11.1%, and 15.4% respectively, $p=0.0001$), with results driven by the reduction in ischemia and reinfarction. There was no difference in the rate of intracranial hemorrhage among the groups, but abciximab was again associated with a greater risk of severe bleeding (4.3%) than either enoxaparin

(3.0%) or UFH (2.2%) (p=0.0005). Based on these studies, the ACCP recommends against the combination of abciximab with half-dose reteplase or tenecteplase, and recommends that streptokinase definitely not be combined with a GP IIb/IIIa inhibitor (3). The ESC similarly recommends against combination therapy (2), while the AHA provides a class IIb recommendation, acknowledging conflicting evidence (1).

Anti-thrombin Agents

Complementing the anti-platelet agents are the anti-thrombins, another commonly used adjunctive therapy for both PCI and fibrinolysis. Unfractionated heparin inhibits the activation of various clotting factors, most notably factor Xa and thrombin. There is relatively little evidence confirming a significant additive benefit of heparin over ASA in combination with streptokinase, and recommendations for its use range from no adjunctive treatment with UFH, to subcutaneous or intravenous administration at various doses (1–3). After having demonstrated superiority to streptokinase in GUSTO-I, fibrin-selective fibrinolytics have been used in combination with intravenous UFH in almost all subsequent trials, and guidelines are unanimous in recommending intravenous administration of a bolus dose followed by a maintenance dose adjusted to keep the activated partial thromboplastin time (aPTT) at 1.5–2 times control (50–70 seconds) for 24–48 hours (1, 2).

There has been considerable interest in using enoxaparin (an LMWH) instead of UFH with fibrinolytics, in part because of its ease of administration and the predictability of its anticoagulant effect. The difficulty in achieving the recommended aPTT with UFH was demonstrated in a trial comparing UFH with enoxaparin, when only 30% of the patients were appropriately anticoagulated between 6 and 12 hours after beginning therapy (64). Furthermore, enoxaparin appears to be superior to UFH in reducing reinfarction or revascularization in patients with unstable angina or non-STEMI (64).

There is also evidence for the benefit of LMWH in STEMI. In patients with STEMI, the ASSENT-3 trial found that in combination with tenecteplase, enoxaparin was a better anti-thrombotic agent than UFH, resulting in a reduction of the primary combined endpoint of death, in-hospital re-infarction, and refractory ischemia from 15.4% to 11.4% ($p<0.001$) (63). Subsequently, however, ASSENT-PLUS revealed a significantly increased risk of intracranial hemorrhage with the administration of tenecteplase with enoxaparin, as opposed to UFH, in patients over the age of 75 (65). As a result of uncertainties raised by ASSENT-PLUS involving bleeding risk, the use of enoxaparin is only recommended as an alternative to UFH in patients < 75 years of age, and even in the non-elderly patients, the recommendation is based on conflicting evidence or opinion (1, 3). The ESC does not make a recommendation regarding its use, citing the need for further investigations (2).

UFH is also recommended for use during primary PCI with weight-adjusted boluses, and was given the highest level recommendation by the ACC and AHA based mainly on the opinion of experts (1). The specific role of LMWH in the invasive management of STEMI is less established. Most trials which have investigated the role of LMWH during PCI have looked at patients undergoing elective angioplasty or PCI for unstable angina or non-STEMI, finding comparable safety and outcomes, but there is a lack of evidence to support replacing UFH with LMWH in STEMI.

Other Ancillary Medications

There are other medications that provide benefit in the setting of STEMI via mechanisms other than reperfusion, or prevention of reocclusion, of the infarct-related artery. Beta-blockers, for one, are thought to be "protective," reducing infarct size and reinfarction when co-administered with fibrinolytics, and reducing mortality when continued long term after AMI. The ACC and AHA provide a class I recommendation for the administration of oral beta-blockers early in the course of an STEMI, with a slightly less robust endorsement of the early use of IV beta-blockers because of conflicting evidence (1). The ESC recommends early IV beta-blockers for particular indications, including tachycardia or hypertension, noting that in most cases, oral administration is sufficient. Enthusiasm for routine, early IV administration was tempered by a meta-analysis which did not show an advantage to early IV over oral administration (66). Nonetheless, beta-blockers improve outcomes and should be administered in a timely fashion, as only 42 patients need to be treated for two years in order to prevent one death. Only fibrinolysis with ASA provide a greater benefit(66).

ACE-inhibitors limit ventricular dilatation and remodeling by interruption of the renin-angiotensin-aldosterone system, and it is well established that oral ACE-inhibitors should be given within the first 24 hours post-infarct to patients who have experienced symptoms of heart failure or are known to have a subnormal ejection fraction

Pearls and Pitfalls

1. STEMI may present without chest pain. The most common symptoms of an "atypical" presentation are dyspnea, diaphoresis, nausea or vomiting, and syncope. Older patients, females, and diabetics are more likely to present atypically. Do not neglect to obtain an early ECG from patients with these symptoms.

2. Bundle branch blocks complicate the electrocardiographic diagnosis of a myocardial infarction. In the setting of ischemic symptoms, a new or presumed new LBBB is an accepted indication for fibrinolytics or PCI, but even patients with old or non-left BBB should be considered for reperfusion therapy.

3. Certain groups of patients are less likely to be offered reperfusion therapy, including women, ethnic minorities, and the elderly, despite demonstrated benefit from intervention. Be particularly vigilant when evaluating these groups for possible ACS.

4. While oral ACE-inhibitors reduce short-term mortality after AMI in patients with impaired ejection fraction or signs of heart failure, early IV administration is contraindicated because of the significant risk of hypotension.

5. There is no evidence that nitrates reduce mortality in the setting of STEMI. They should be used for specific indications, including ongoing ischemia or pulmonary edema, rather than given routinely.

Key Concepts

1. All patients who present with STEMI within 12 hours of symptom onset should be evaluated for emergent reperfusion therapy. Patients who would likely benefit more from PCI than from fibrinolysis include those with signs of heart failure, those who present more than three hours after symptom onset, and those who are at increased risk of bleeding complications from fibrinolytics.

2. The fibrin-specific fibrinolytic t-PA offers a small but significant mortality benefit over streptokinase. The newer fibrin-specific agents, e.g., reteplase and tenecteplase, are no more efficacious than t-PA, but offer the advantage of bolus dosing.

3. The role of "facilitated PCI," using various combinations of fibrinolytics and glycoprotein IIb/IIIa inhibitors prior to planned PCI, remains under investigation. To date, there is no convincing evidence of benefit from such an approach.

4. Abciximab is the best studied of glycoprotein IIb/IIIa inhibitors in STEMI, and there is evidence that its use in patients undergoing PCI reduces the need for short- and mid-term ischemia-induced revascularization. This benefit may be greater if abciximab is started before arrival in the catheterization laboratory.

5. Oral beta-blockers, when initiated promptly after AMI and continued long-term, reduce mortality. The additional benefit of early IV administration is not significant, although hypertension and tachycardia are accepted indications.

(2) (the ACC and AHA also consider an anterior MI a class I indication (1)). ACE-inhibitors should not be administered in the setting of absolute or relative hypotension, and intravenous administration is contraindicated because of the risk of inducing hypotension.

Nitrates, while commonly used, have not demonstrated an outcome benefit in the setting of STEMI. Nitrates might be expected to reduce infarct size and improve outcome, as they diminish preload, thereby decreasing wall stress and myocardial oxygen demand. Additionally, there is direct vasodilatation of coronary arteries, potentially increasing collateral blood flow to ischemic myocardium. Despite these theoretical advantages, the GISSI-3 and ISIS-4 megatrials (with a combined total of more than 77,000 patients) did not reveal a 4–6 week mortality benefit for nitrates initiated in the acute phase of AMI (either oral or IV) and continued for 4–6 weeks (67, 68). They do, however, appear to be safe in the absence of hypotension, and while there is not a role for routine administration, nitrates are recommended for ongoing ischemia, pulmonary edema, or hypertension (1, 2). Significantly, nitrates should be used only with extreme caution in the setting of RV infarct, as they reduce RV preload, and may therefore have very adverse hemodynamic consequences (1).

Conclusions

Efforts to improve the outcome of STEMI continue, with much of the recent work focusing on strategies to increase the availability of reperfusion therapy. Research also continues on optimizing fibrinolytic agents, PCI techniques, and adjunctive therapy. With such a large volume of data published on the topic, clinical practice guidelines become an important source of information and direction for the clinician, promoting the application of current evidence to the bedside care of these patients.

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(References 1-4 contain relevant practice guidelines)

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Atrial Fibrillation

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Abstract

In 2000, some 2.3 million Americans were affected by atrial fibrillation, and that number is expected to rise as our population ages. Atrial fibrillation is both a reflection of active physiologic stressors on the body and a marker of future cardiac disease progression. The disorganized atrial activity that characterizes atrial fibrillation affects cardiac function, metabolic demand, and quality of life. However, our understanding of the etiology and treatment of this condition continues to advance with the result of recent large-scale clinical trials.

Diabetes, hypertension, congestive heart failure, valvular disease, and myocardial infarction are all risk factors in the development of atrial fibrillation. And the diagnosis confers a five-fold increase in the incidence of stroke. (Patients at increased risk for stroke include those with congestive heart failure, hypertension, age greater than 75, diabetes, and previous stroke.) Anticoagulation is a critical action in most cases of atrial fibrillation, as data show a 68% relative risk reduction of stroke when patients are treated with warfarin. Prior to recent trials, achieving sinus rhythm was thought to invariably improve symptoms, cardiac function, and mortality. The adverse effects of antiarrhythmic medications are now being recognized, and treatment strategies emphasizing ventricular rate control have been recommended in recent clinical practice guidelines. This shift in thinking is influencing both outpatient and emergency department management. Controlling the ventricular rate in atrial fibrillation increases cardiac output, decreases the metabolic demand of the heart, and avoids the potentially dangerous side effects of rhythm-control drugs. Rate-control agents should be selected based on the clinical profile of individual patients. A well-chosen subset of patients may benefit from either chemical or electrical cardioversion; this appears to be a reasonably safe procedure and can be accomplished on an outpatient basis.

Understanding causal etiologies, managing risk for stroke (and need for anticoagulation), addressing rate, and assessing the risks of cardioversion are key elements in a comprehensive approach to atrial fibrillation.

Key Words: Fibrillation, atrial; arrhythmia.

Introduction

ATRIAL FIBRILLATION (AF) is the most common arrhythmia in the adult population (1). The presence of atrial fibrillation may be a reflection of active physiologic stressors on the body, as well as a direct influence on future disease progression. The disorganized atrial activity itself affects cardiac function, metabolic demand, and quality of life. Conceptually, AF should be thought of as both a signal of underlying disease and a condition per se unto itself.

The presentation and management of AF will vary according to the setting and circumstances in which it is encountered. The emergency physician may face a patient *in extremis*, hypotensive and unresponsive, clearly requiring rapid evaluation and treatment of the arrhythmia. The internist may have difficult questions regarding the risks and benefits of taking warfarin daily. In both cases, the provider must be aware that decisions made today can have immediate consequences, including clinical deterioration or embolic stroke. Long-term effects, such as atrial remodeling, may also be determined by choices made in the clinic or emergency department (ED). Furthermore, recent evidence has led to revision or reversal of many previously held beliefs regarding how best to manage AF. This article will review the short-term and long-term strategies in managing this widespread condition.

Epidemiology

In 2000, it was estimated that 2.3 million Americans were affected by AF, and the number is expected to more than double over the next fifty years as our population ages (2). Data from the Framingham cohort show a lifetime risk of developing AF of one in four for adults over age 40 (1). Adjusting for co-morbidities within this cohort, the presence of the arrhythmia itself confers an independent relative risk of death of 1.5 and 1.9 for men and women, respectively (3). One of the most debilitating consequences of the disease is the accompanying risk of stroke, which occurs in an es-

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timated 60,000 patients with AF per year (2). Aside from an increase in morbidity and mortality, patients with AF often experience changes in their quality of life owing to symptoms such as palpitations and decreased exercise tolerance (4, 5). The scope of these challenges will grow as our population ages and our understanding of the disease expands.

Etiology / Pathophysiology

When the atria are in fibrillation, contraction occurs at rates of 350–900 per minute. The AV node may conduct these impulses to the ventricles at 90–170 beats per minute, and often higher. There are several complementary and competing theories regarding the pathophysiology of AF initiation and propagation. AF may be triggered by a premature atrial beat, with the pulmonary vein shown to be a frequent source of ectopy (6, 7). Atrial flutter has also been shown to trigger AF (8). The maintenance of the arrhythmia is classically described using a model of multiple wandering reentry wavelets propagating through atrial myocardium (9, 10). Multiple fronts of excitation colliding within the atrial tissue extinguish or augment one another. The wavelet collisions result in chaotic re-excitation throughout the atria. These re-entry phenomena can occur at rates exceeding the response capability of the myocardium, resulting in fibrillation (8). As this pattern of diffuse re-excitation continues over the course of time, it is believed that both electrophysiologic and structural remodeling of the atria occurs. This remodeling creates a milieu for the arrhythmia to persist—hence the expression "atrial fibrillation begets atrial fibrillation." Paroxysmal AF thus proceeds to persistent (that is, continuous but potentially convertible) AF and onward to permanent AF, refractory to antiarrhythmic efforts.

The disease states that predispose patients to AF have been well studied. Benjamin and coauthors demonstrated diabetes, hypertension, congestive heart failure, valvular disease, and myocardial infarction to be risk factors in its development (11). Over 8% of patients newly diagnosed with clinical hyperthyroidism are also found to be in AF or flutter (12). One study showed a correlation between alcohol consumption and AF (13), but others have failed to show any correlation or have demonstrated a protective effect with imbibing (14); this relationship therefore continues to be an open question. Echocardiography indicated increased left atrial size to be a structural predisposition in the subsequent development of AF (14–16).

As mentioned, the presence of AF has prognostic significance for the patient. Its presence is reported to confer up to a five-fold increase in the incidence of stroke, with the cumulative risk averaging out to approximately 5% per year (17). Furthermore, an ischemic stroke in the presence of AF is almost twice as likely to be fatal than strokes occurring in sinus rhythm (18). AF influences further cardiac disease progression through its contribution to development of congestive heart failure. The loss of "atrial kick" from the arrhythmia decreases stroke volume by as much as 20% (19). Tachycardia-related cardiomyopathy in patients with poor rate control may further depress cardiac reserve (20). The presence of AF together with congestive heart failure increases mortality and hospitalization rates compared to heart failure patients in sinus rhythm (21). The relationship between AF and congestive heart failure highlights the broader question of whether AF is an active participant or a passive marker of overall cardiac disease progression.

Atrial Fibrillation and Risk of Stroke

Stroke risk in AF varies across a range of ages and cardiovascular co-morbidities. Therefore, risk-stratification tools have been developed to determine which patients should be considered for anticoagulation. One method used for identifying patients at higher or lower risk for stroke is the CHADS$_2$ risk index (**C**ongestive heart failure, **H**ypertension, **A**ge ≥ 75, **D**iabetes, and **S**troke or transient ischemic attack history) (22), which is an amalgamation of the conclusions from two studies, the Stroke Prevention in Atrial Fibrillation study, and the Atrial Fibrillation Investigators study (18, 23). The authors used clinical features to determine the patient's risk of stroke, with double weight given to a history of previous stroke (Table 1). A CHADS$_2$ score of 0 correlates with an adjusted stroke rate of 1.9 per 100 patient-years; a score of 6 predicts a stroke rate of 18.2 per 100 patient-years. The CHADS$_2$ index was shown to estimate stroke risk more completely than either of the other two

TABLE 1
CHADS$_2$ Clinical Classification Scheme for Predicting Stroke (22)

Stroke Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75	1
Diabetes Mellitus	1
Stroke History	2
	6

classification schemes alone. $CHADS_2$ has recently been shown to be more robust compared to other stratification schemes, but other decision rules have been proposed (24–26). Ideally, these risk stratification schemes allow the clinician to individualize therapeutic choices by balancing the patient's risk of developing a stroke with the risks and benefits of specific anticoagulation agents. As an example, certain patients may be appropriate candidates for more conservative anticoagulation strategies, such as using aspirin alone (27).

Chemical assays may soon play a role in stroke risk stratification. C-reactive protein is being investigated as a marker of inflammatory burden in certain chronic conditions, including coronary artery disease and stroke (28). It has been found to be elevated in patients experiencing new-onset arrhythmias during the immediate post-cardiopulmonary bypass period (29, 30). In the future, levels of this substance may assist in determining stroke risk in patients with AF (31).

Diagnosis

Electrocardiographic manifestations of AF include irregularly irregular R-R intervals, absence of P waves, and fibrillatory waves of varying morphology. These F waves are best seen in leads V1, II, III, and aVF (32). Although the diagnosis of AF is straightforward in most cases, the practitioner should be aware of potential pitfalls. The patient with an electronically paced rhythm, digoxin toxicity, or heart block may have regular R-R intervals. This regularity may lead to the false conclusion that an atrial arrhythmia is absent, causing the clinician to overlook a potentially catastrophic condition. Multifocal atrial tachycardia and wandering atrial pacemaker can both have irregular ventricular responses; careful attention to the presence of P waves of differing morphology will elucidate their true identity. Likewise, rapid ventricular response can make visualizing the P waves difficult. One strategy that may be used in this setting is to increase the speed of the electrocardiogram (ECG) rhythm strip, to better visualize fibrillation waves (33). Another approach, when the diagnosis continues to be unclear, is a trial of adenosine. During the transient blockade of the AV node, the underlying rhythm can often be appreciated. Even though adenosine appears to be safe for this indication, caution should be exercised when using it in the setting of possible accessory pathways, specifically in an irregular wide-complex tachycardia (34).

Recognition of AF mandates investigation into its etiology, its previous course, and likely outcome. A complete history and a previous ECG will help determine if the arrhythmia is new-onset o chronic. Risk factors for stroke and bleeding wil guide the risk/benefit analysis of using anticoagulation. As mentioned previously, AF can be a signal for the presence of underlying pathology, an the history and physical exam will focus the searcl for an underlying cause of the rhythm change With new-onset AF, one should consider pulmonary embolism, cardiac ischemia, congestiv heart failure, "holiday heart" (due to arrhythmogenicity in binge ethanol consumption), increase vagal tone (35), and hyperthyroidism, amon many possibilities (Table 2). Even after a thorougl workup, 30% or more of chronic AF remains idiopathic (36). To determine why a patient's chroni AF has a rapid ventricular response, consider conditions that may increase sympathetic tone or wor directly on the AV node: fever, dehydration, gastrointestinal (GI) bleed, sepsis, medication non compliance, and many more.

Treatment

Treatment of AF is directed by the following factors

(1) patient stability
(2) underlying etiology of arrhythmia
(3) symptoms
(4) ventricular rate
(5) risk factors for stroke

The first step in caring for AF is to recognize critically ill patient and rapidly address the unstable rhythm. The Advanced Cardiac Life Suppor (ACLS) guidelines from the American Heart Assc ciation state that the provider must be prepared fc immediate cardioversion with any ventricular rat over 150, and should take action as the clinical picture dictates (37). Pre-medication of the patier prior to any shock delivery with sedatives an analgesia is ideal, but the provider must take int consideration the patient's physiologic reserve an ability to tolerate the medication. The sequence c synchronized cardioversion using monophasi waveforms proceeds starting at 100J (50J for atri flutter), increasing to 200J, 300J, and finally 360.

TABLE 2
Causes of Atrial Fibrillation

Alcohol intake
Congestive heart failure
Electrocution
Electrolyte abnormalities
Hypertension
Hyperthyroidism
Idiopathic
Increased sympathetic states
    Gastrointestinal bleed
    Hypovolemia
Ischemia/Infarction
Medications
Myocarditis
Pericarditis
Pulmonary embolism
Surgery
Valvular heart diseas

One study of 64 patients suggested that an energy level of 100J is too low to convert most patients, and recommended starting at 200J (38). Biphasic devices deliver current at a lower energy level, and have device-specific recommendations. Recognize that instability applies to both vital signs and the overall clinical status: pulmonary congestion, altered mental status, and severe chest pain are typically considered signs of decompensation. As discussed above, the physician must recognize and address any underlying physiologic imbalances that may have precipitated the arrhythmia. Exploring possibilities such as infection, a pulmonary process or intravascular volume loss will prevent a false sense of security from delaying definitive treatment.

Rate or Rhythm: Which Strategy Is Best?

Prior to several recent large trials, it was assumed (but unproven) that patients with persistent AF received benefit from aggressive treatment to maintain a sinus rhythm. Intuitively, maintaining sinus rhythm would seem preferable for the sake of improved cardiac function and symptom control. However, investigators began to suspect that the adverse effects of antiarrhythmic medications might weigh against the overall benefit of this treatment strategy (39). In contrast, an approach focused on maintaining a lower heart rate, along with adequate anticoagulation, might be a preferable alternative.

The landmark AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial enrolled 4,060 patients with AF and risk factors for stroke or death (40). Patients were randomized into rhythm- or rate-control groups. The investigators found no difference between the two groups in death or composite morbidity; an increase in subsequent hospitalization rates was found in the rhythm control group (80.1% vs. 73%). Most surprisingly, the strategy of maintaining sinus rhythm did not lower the rate of ischemic stroke over rate-controlled patients. The authors concluded that controlling the ventricular rate, along with anticoagulation, was at least as effective in preventing morbidity and mortality in patients with AF as traditional antiarrhythmic strategies (41, 42). This outcome equivalence between the two strategies was also established in the European RACE trial of 522 patients (43), and subsequent studies (44). Focusing on rate rather than rhythm has also been shown to be more cost-effective (45, 46).

The AFFIRM data demonstrate that patients presumed to be maintained in sinus rhythm have stroke rates similar to those patients in rate-controlled AF. Possible explanations of this finding include medication inefficacy, non-compliance, or undetected paroxysms of AF with thrombus formation in patients believed to always be in sinus rhythm. This last point is supported by a recent study of patients with implanted pacemakers who were maintained on antiarrhythmic medications and who demonstrated a significant number of asymptomatic episodes of AF, some lasting greater than 24 hours (47). It follows that freedom from symptoms in patients with known paroxysmal or permanent AF may not be a guarantee against thrombus formation. This may be especially true in patients using rate-lowering agents, so that ventricular response may be moderately suppressed, obscuring recognition of the exact moment the arrhythmia began. In any ambiguous situation, a cardioversion plan without adequate anticoagulation should be carefully scrutinized.

The evidence supporting an outpatient strategy of rate-control with anticoagulation has gained credence since these studies were published, and were incorporated into the clinical guidelines for managing AF by the American College of Physicians. This shift in thinking also relates to emergency physicians who may be inclined to aggressively cardiovert stable patients in AF; the benefits of acute rhythm control may not balance the risks of the procedure.

Rhythm Strategies

There are certain circumstances where the physician may consider elective cardioversion (either chemical or electrical). Symptoms affecting quality of life, younger patients with a lower risk of thromboembolism, or patient preference may all be reasons to attempt cardioversion. Failure of rate control measures or contraindications to anticoagulation may also push the clinician towards sinus rhythm maintenance. Before embarking on this approach, however, the risks associated with cardioversion should be evaluated. The physician must assess the possibility of thrombus in the fibrillating atria, which may dislodge upon reversion to sinus rhythm, a risk estimated to be less than 1% over eight weeks following cardioversion (48). The traditional teaching has been that patients in fibrillation for less than 48 hours have a low risk of thrombus formation. But, the risk is not zero, and one study has shown echocardiographic evidence of thrombus in the left atrial appendage less than three days after the arrhythmia begins (40). As mentioned above, patient history may not be a reliable indicator for the absence of AF in the recent past.

The procedure for electrical cardioversion is carried out in a similar fashion to that of the unstable patient, except it occurs in a controlled environment with judicious use of sedation. In one multicenter-ED-based trial of 388 patients, electrical cardioversion in a low-risk cohort had an 86% success rate, with few complications from the procedure. In this study, long-term follow-up assessing thromboembolism occurrence was not performed, and further investigation into the safety of this strategy should be conducted (49).

With chemical cardioversion, there are several approved agents to choose from. In a meta-analysis conducted during their guideline development, the American College of Physicians found that ibutilide, flecainide, dofetilide, propafenone, and amiodarone all had strong evidence supporting their safety and efficacy, with ibutilide having an odds ratio of conversion equal to 30.7:1 over placebo (50). Table 3 details dosing and side effects for commonly used cardioversion agents. The chemically cardioverted patient must be observed after the procedure for subsequent medication-induced arrhythmias, such as *torsades de pointes*. Given these considerations, along with the moderate failure rate of the procedure (10–30%) and a high chance of recurrence, the candidates for elective cardioversion of AF must be thoroughly educated regarding the risks and benefits of this procedure before making a decision (51–53).

Immediately following electrical or chemica cardioversion, there is a period of "atrial stunning," a stasis environment that may predispose to thrombus formation for up to two weeks following the procedure (54). The American Academy o Family Physicians/American College of Cardiology (AAFP/ACP) guidelines recommend three weeks of anticoagulation prior to cardioversion followed by four weeks of anticoagulation in orde to avoid these risks. An alternate strategy recommended is evaluation by trans-esophageal echocardiography, followed by three weeks of anticoagulation during the period of atrial stunning (see "Guidelines" section below).

Rate-Control Agents

Controlling the ventricular rate in AF increases cardiac output, decreases the metabolic demand of the heart, and avoids the potentially dangerous side effects of rhythm-control drugs. The selection of a medication to control rate, either in the ED or for the outpatient, should be made in light of the clinica circumstances. Each agent also has the potential to spontaneously convert the patient back to a sinus rhythm, so risk-stratification for thromboembolic disease should be performed before choosing a drug

Nondihydropyridine calcium channel antagonists are commonly used rate agents. They are active at the AV node and relatively safe, and have a

TABLE 3

Medications for Cardioversion of Atrial Fibrillation to Sinus Rhythm

Drug	Dosage	Route	OR of conversion over placebo	Side Effects
Ibutilide	1 mg over 10 min	IV	30.7	QT prolongation, *torsade de pointes*
Flecainide	200–300 mg PO/ 1.5–3.0 mg/kg IV over 10–20 min	Oral/IV	13.2	Hypotension, rapid atrial flutter
Propafenone	450–600 mg PO/ 1.5–2.0 mg/kg over 20 min	Oral/IV	3.9	Hypotension, rapid atrial flutter
Amiodarone	1.2–1.8 g/day oral divided until 10g total 5–7 mg/kg IV over 60 min, then 1.2–1.8 g/day IV infusion until 10 grams	Oral/IV	3.2	Hypotension, bradycardia, QT prolongation, *torsade de pointes*, GI complaints
Dofetilide	Renal dosing	Oral	6.7	QT prolongation, *torsade de pointes*

OR = Odds ratio

demonstrated efficacy in decreasing ventricular rate in comparison to other agents. Diltiazem and verapamil are the agents most commonly used. There may be apprehension about giving a calcium channel blocker in the setting of decompensated heart failure, as the risks of hypotension are thought to be compounded in patients with compromised cardiac function. There have been several studies which have not shown this assumed effect; improvement of stroke volume with increased diastolic filling time may be a reason why further clinical deterioration tends not to occur (55–57). The use of diltiazem rather than verapamil may decrease the incidence of hypotension (58). Another strategy advocated is "priming" the patient with intravenous calcium prior to administration of the calcium channel blocker. By first infusing calcium, the peripheral vasodilatory effects of the calcium channel blocker may be attenuated without affecting AV nodal activity (59–61). This pretreatment effect has been shown in trials using verapamil, but its use with diltiazem has yet to show a significant benefit (62). A dose of 3 mL of calcium chloride or 5 mL of calcium gluconate is recommended.

In the patient with rapid AF presenting with potential myocardial ischemia, a beta blocker is an excellent choice. It is an effective agent for rate control and has mortality benefit in the setting of acute coronary syndrome. A short-acting drug, such as esmolol, can be titrated if hypotension is a concern. Thyrotoxicosis, while not often diagnosed in the emergency department, is another condition for which a beta blocker may be beneficial. Propranolol is considered a first-line agent because of its effects on rate and blood pressure, as well as its activity in blocking peripheral conversion of T_4 to T_3. Always consider contraindications (e.g., bronchospasm) before using a beta blocker.

Caution must be used when using a calcium channel blocker and a beta blocker simultaneously (63). Hypotension, bradyarrhythmias, and AV nodal conductions disturbances have been reported in patients on oral formulations (64). The combined negative chronotropic effects of the medications are further enhanced by reciprocal inhibition of their hepatic clearance (65, 66). This negative synergistic effect may put the acute patient at risk for heart block if the two classes of medications are used concomitantly, especially in elderly patients with left ventricular dysfunction.

Digoxin has historically been used as a rate-controlling agent, especially in heart failure where its inotropic effects could be maximized. Despite this theoretical advantage, its usefulness in the acute setting is limited. Peak rate control effects may not be seen for hours after loading the drug. If there is an increase in the patient's sympathetic drive (often the case in the setting of hypovolemia, cardiac ischemia, or infection), the drug's vagotonic mechanism of AV nodal action will be ineffective (67). Given its significant side effect profile, digoxin should be considered at most a second-line agent for rate control (68).

Amiodarone, a medication approved for treatment of ventricular arrhythmias, has effective beta-blocking properties and has been shown to rapidly control rate in the new-onset AF patient (69). Current ACLS guidelines recommend amiodarone for rate control of AF in stable patients with known ejection fractions of less than 40% (70). Additionally, amiodarone may be preferable to calcium channel blockers when adequate blood pressure is a concern. In a study of 60 intensive care unit patients in rapid AF, amiodarone was shown less likely to cause hypotension than diltiazem (although the calcium channel blocker was superior in controlling ventricular rate at 24 hours (71). Amiodarone is also useful in the setting of a wide-complex tachycardia of uncertain origin, where the drug's antiarrhythmic properties are active against both ventricular and supraventricular sources (72). A previous drawback to its use was perceived expense; generic formulations of amiodarone have recently become available and may reduce this cost.

Magnesium has also been shown to be effective at rate control in AF. When given as bolus followed by infusion, it was shown to have rate-control effects comparable to those of amiodarone, and significantly higher rates of reversion to sinus rhythm than diltiazem (57% vs. 22%) (73, 74). Magnesium's efficacy and low cost make it an attractive rate-control option.

When giving any rate-control agent, it is important to consider the potential to convert the rhythm back to sinus—a dangerous occurrence in patients unprotected from embolic stroke (75). Although the cessation of AF may be unrelated to the medication, it is clear that these agents can cause reversion to a sinus rhythm. The conversion risk for each drug is difficult to estimate, but the clinician is still advised to consider this effect when rate-controlling a patient not on anticoagulation (Table 4).

In cases of AF refractory to pharmacologic rate control, AV nodal ablation and permanent pacemaker placement may be required for definitive rate control.

Anticoagulation

Since the advent of electrical cardioversion by Lown in the 1960s (76–78), it was recognized that

TABLE 4

Rate-Control Medications for Atrial Fibrillation with Rapid Ventricular Response

Drug	**Loading Dose**	**Maintenance Dose**	**Onset**	**Side Effects**	**Patient Population**	**Conversion Rate Acute**	**Remarks**
Diltiazem	0.25 mg/kg IV over 2 min	5–15 mg/hr	2–7 min	Hypotension, decreased AV nodal conduction	Stable patients	50–66%	Can "prime" with calcium to prevent hypotension
Metoprolol	2.5–5 mg IV bolus over 2 min up to 3 doses	N/A	5 min	Hypotension, AV nodal conduction disturbances, bronchospasm	Ischemia, thyrotoxicosis	57%	Avoid using together with CCB
Esmolol	0.5 mg/kg over 1 min	0.05–0.2 mg/kg/min	5 min	Hypotension, AV nodal conduction disturbances, bronchospasm	Ischemia, thyrotoxicosis	80%	Easy to titrate in patients with border-line BP
Magnesium	1 gram over 20 min	Variable	5 min	Hypotension	Mg-depleted (i.e., alcoholics)	60–78%	Inexpensive
Amiodarone	150 mg IV bolus over 10 min	1 mg/min for 6 h, then 0.5 mg/min for 18 h	20 min	Hypotension	Wide complex tachycardia, borderline BP	43–80%	Newer generi formulations available. Not approved for supra-ventricular arrhythmias
Digoxin	0.25 mg IV every 2 hours up to 1.5 mg	N/A	2 hours	Digoxin toxicity, heart block	Refractory to first-line therapy	Similar to placebo	Not recom-mended as first-line agent

CCB = calcium channel blockers; Mg = magnesium.

anticoagulation prevented embolic events after the procedure (79, 80). Data pooled from multiple studies show a relative risk reduction for stroke of 68% in patients treated with warfarin (an absolute risk reduction of 3.1%) (81). In the AFFIRM trial experience, it was found that most patients with stroke and AF had either sub-therapeutic anticoagulation or had discontinued their anticoagulation medications altogether. Recent trials have examined the use of a combination strategy of employing lower levels of anticoagulation combined with antiplatelet agents, and the results show an encouraging trend towards better outcomes and fewer side effects (specifically vascular death, transient ischemic attack, and nonfatal stroke or systemic embolism) (82). This strategy may become more widespread in the near future, pending results of investigations into bleeding rates with antiplatel and anticoagulant combination therapy (83, 84 As emphasized above, it is critical that the physician identify patients at high risk for stroke to fo mulate an anticoagulation strategy.

While not officially approved for anticoagul tion in the setting of AF, the use of low-molecula weight-heparin (LMWH) has been investigated as bridge to outpatient oral anticoagulation (85, 86 One small study of 18 patients showed a trend t wards decreased cost and length of stay whe LMWH was used in an ED-based cardioversio strategy (87), and another study suggests that usin LMWH may shorten recommended anticoagulatio times prior to cardioversion (88). As the indication for these versatile drugs continue to expand, we ca expect more data on this topic in the future.

Pearls and Pitfalls

- Diltiazem can be safe for patients with LV dysfunction. Consider pre-treatment with calcium to avoid hypotension.
- Avoid using beta blockers and calcium channel blockers simultaneously in the same patient.
- Consider digoxin a second-line agent in cases refractory to calcium channel or beta blockade.
- Keep in mind the intrinsic ability of some rate-controlling agents to convert the arrhythmia back to sinus—and be prepared for the consequences.
- If the patient is taking digoxin, cardioversion may inadvertently lead to heart block.
- Patient history may not always be a reliable indicator of the initiation of atrial fibrillation.

Key Concepts

- The presence of atrial fibrillation or a rapid ventricular rate may be a sign of an extra-cardiac physiologic disturbance (ischemia, GI bleed, pulmonary embolism, hypothermia, electrolyte disturbances).
- Risk-stratifying patients using a clinical decision tool such as $CHADS_2$ is helpful in assessing the benefit of chronic anticoagulation.
- Rate-control agents may yield additional benefit in certain situations, such as cardiac ischemia and hypotension.
- Before cardioverting a patient in the emergency department, weigh both the long- and short-term benefits against the risks of embolic stroke and other complications.

There are emerging alternative options to traditional anticoagulation agents that may be of use in the coming years. A new class of medication, direct thrombin inhibitors, has been investigated in industry-sponsored European trials (89). The studies have shown their equivalency to warfarin in prevention of stroke in AF patients. The advantage of this medication (ximelagatran) is that it is administered in a fixed dose, with no need for frequent coagulation monitoring. Although available in some European markets, it is not currently approved for use in the United States.

A new device, PLAATO® (ev3 Inc., Plymouth, MN), is positioned by a catheter into the left atrial appendage, theoretically preventing thrombus from forming. It is not known if this device could preclude the use of anticoagulants in patients at risk for thromboembolic disease.

Treatment Guidelines

Groups involved in creating guidelines for the treatment of AF include the American College of Cardiology, American Academy of Family Physicians, American College of Physicians, and American College of Chest Surgeons. The most recent guidelines, formulated by a joint panel of the ACP and AAFP, make the following recommendations (50) (with the associated evidence grades in parentheses):

- Rate control with chronic anticoagulation is the recommended strategy for most atrial fibrillation patients (Grade 2A)
- Use warfarin unless patients are in a low-risk group or have contraindications for its use (Grade 1A)
- Atenolol, metoprolol, diltiazem and verapamil are recommended for rate control as an outpatient; digoxin should be considered second-line therapy for patients who do not exercise (Grade 1B)
- For patients opting for cardioversion, direct current (Grade 1C+) or pharmacologic conversion (Grade 2A) are both appropriate options.

- Either transesophageal echocardiogram (TEE) with early cardioversion, or three weeks of anticoagulation prior to cardioversion, are acceptable strategies to minimize stroke risk in patients electing cardioversion. Both strategies are followed by three to four weeks of anticoagulation (Grade 2A)
- Antiarrhythmic medications are generally not recommended, as risks likely outweigh benefits (Grade 2A)

Since more research is being conducted on management strategies for atrial fibrillation, clinical policies from other professional bodies may be forthcoming, helping to synthesize the vast amount of literature on the topic.

Conclusion

As the incidence of atrial fibrillation increases and our therapeutic options continue to expand, the primary care physician must think a step beyond the urgent clinical issues at the bedside when a patient presents with the disease. He or she must recognize the underlying pathophysiology that the arrhythmia is built upon, as well as the potential acute and long-term hemodynamic and neurological consequences of not employing a comprehensive strategy. Pursuing root causes, managing risk for stroke, addressing rate, and weighing the risks of cardioversion form a framework for developing such a strategy.

Practice Guidelines

"Management of Newly Detected Atrial Fibrillation: A Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians"—2003 (50)

"ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation"—2001 (32)

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Treatment of Tension-Type Headache with Botox:

A Review of the Literature

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Abstract

Botulinum toxin has been shown to effectively treat several types of neurological disorders. It has recently been evaluated for the treatment of tension-type headaches in patients who are unable to tolerate or cannot benefit from standard therapies. Most of the open design studies seem to present positive results. However, the randomized, double-blind, placebo-controlled studies present contradictory results for the efficacy of botulinum toxin. Based on these data, further controlled trials of botulinum toxin are needed to evaluate its effects on tension headaches and to determine optimal injection sites, doses, and frequency of treatments.

Key Words: Botox, tension-type headache, headache.

Introduction

RECENT STUDIES demonstrating the effectiveness of botulinum in treating several disorders related to muscle spasticity and pain suggest a potential role for this agent in headache treatment. Botulin or botulinum toxin (BT), a polypeptide produced by the anaerobic bacterium *Clostridium botulinum*, is one of the world's deadliest substances. It is best known as a source of food poisoning; its ingestion in spoiled food can lead to death caused by muscle paralysis. The toxin interferes with presynaptic vesicular release of acetylcholine from nerve endings and interrupts neuromuscular transmission (1, 2). It also exerts a blocking action on the parasympathetic nervous system, and may inhibit release of other neurotransmitters or affect transmission of afferent neuronal impulses (2, 3).

Purified toxin injected locally into muscles causes paralysis for up to 3 – 4 months, after which nerve endings regenerate and the toxin's clinical effects wear off (2, 4). The ability of this agent to reversibly alter muscle strength, with few systemic side effects, suggests its potential therapeutic usefulness in such diverse conditions as post-stroke, congenital spasticity or contractures, dystonias, regional myofascial pain syndromes, and other disorders that involve pathologic muscle hyperactivity. BT is also being studied as a treatment for a variety of pain conditions, especially those in which heightened muscle tension is believed to play a role (2). This review summarizes evidence to date regarding the use of BT in treating tension-type headaches.

The International Headache Society (IHS) began developing a classification system for headaches in 1985. Finalized in 1988, this system includes a tension-type headache category, further defined as either episodic or chronic. Headache categories are also defined by whether they are associated with pericranial muscle disorders. Episodic tension headache usually is associated with a stressful event. This headache type is of moderate intensity, self-limited, and usually responsive to nonprescription drugs. Chronic tension headache often recurs daily and is associated with contracted muscles of the neck and scalp. This type of headache is bilateral and usually occipitofrontal. Tension-type headache is the most common type of chronic, recurring head pain. In the past, pain eti-

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ology was presumed to be the muscular contraction of pain-sensitive structures of the cranium, but the IHS intentionally abandoned the terms "muscular contraction headache" and "tension headache," because no research supports muscular contraction as the sole pain etiology. Pain onset in tension-type headache can have a throbbing quality and is usually more gradual than onset in migraines. Compared with migraines, tension-type headaches are more variable in duration, more constant in quality, and less severe (5).

The IHS diagnostic criteria for tension-type headaches state that two of the following characteristics must be present: pressing or tightening (nonpulsatile quality), frontal-occipital location, and/or bilateral with mild/moderate intensity. Tension-type headache history is usually as follows: duration of 30 minutes to 7 days; no nausea or vomiting (anorexia may occur); photophobia and/or phonophobia; a minimum of 10 previous headache episodes; fewer than 180 days per year with headache; bilateral and occipitonuchal or bifrontal pain; pain described as "fullness," "tightness/squeezing," "pressure," or "bandlike/viselike," which may occur acutely under emotional distress or intense worry; insomnia; pain often present upon rising or shortly thereafter; pain not aggravated by physical activity; muscular tightness or stiffness in neck, occipital, and frontal regions; duration of more than 5 years in 75% of patients with chronic headaches; difficulty concentrating; and no prodrome. A new headache onset in elderly patients should suggest etiologies other than tension headache (5).

The physical examination serves mainly to exclude the possibility of other headache causes. Vital signs should be normal. Tenderness may be elicited in the scalp or neck, but no other positive physical exam findings should be noted. Pain should not be elicited over the temporal arteries or positive trigger zones. Some patients with occipital tension headaches may manifest tender upper cervical muscles. Pain associated with neck flexion and stretching of paracervical muscles must be distinguished from nuchal rigidity associated with meningeal irritation. The causes include stress and/or anxiety. Stress may cause contraction of neck and scalp muscles, although no evidence confirms that the origin of pain is sustained muscle contraction. Other causes include poor posture, depression, and psychological or social problems (5).

Discussion

A large number of clinical studies are available for the evaluation of botulinum toxin in the treatment of tension-type headache. The results however are contradictory. After the first negative report of Zwart et al., who in an open study injected only the temporalis muscle on one side of the head and did not find an improvement in any of 6 patients treated with 30–40 U of Botox, all later case reports and open studies presented positive results (6, 7). Krack et al. first described a patient with tension-type headache who became pain-free after injection of 160 U of Dysport (European brand name for botulinum toxin) (7, 8). Relja treated 10 patients with 15–35 U of Botox using individual injection sites. She found a significant reduction in headache duration, pain intensity and pain sensitivity (7, 9). In a further 24 patients treated using the same study design, Relja found a lasting effect in long-term use over 15 months. This may be because the repeat injections had a step-like therapeutic effect: the consecutive therapeutic effect of each injection built on the effect previously achieved (7, 10). This was further seen in a study conducted by Ondo et al. They conducted a double-blind, placebo-controlled, parallel study of botulinum toxin type A for chronic tension-type headache and chronic migraine headache in 60 patients. The primary efficacy point was the number of headache-free days as assessed by diary for 12 weeks after Botox injection. Secondary efficacy points included global impressions, the use of abortive headache medications and palpation. After recruitment, subjects kept dairies for 4 weeks prior to randomization, at which time they received either 200 U of Botox or matching placebo and were followed. After the week-12 evaluation, patients were offered 200 U of Botox (open-label), and were similarly followed for another 12 weeks. Over a 12-week period after injections, headache-free days had improved in the Botox group from week 8–12 and tended to improve strongly over the entire 12-week period, but did not meet a significance criterion. The subject global impressions, subject change in headache impressions, and investigator global impressions all improved in the Botox group as compared with the placebo group. At week 24 (open label), there were more headache-free days in the twice-Botox-treated group compared with the once-injected group. Therefore, the study showed that Botox may help chronic daily headache and appears to have a cumulative effect with subsequent injections (11).

In an open study, but using a standardized injection design, Schulte-Mattler et al. reported on the use of Dysport (total of 200 U) in 9 patients with chronic tension-type headache not sufficiently responding to physical therapy and pharmacotherapy. Patients kept a headache diary from which the area under the headache curve (AUC) 4 weeks before and after treatment was calculated. After a 4-week run-in phase, equal doses of 25 units of Botox were injected into the frontalis, temporalis, occipitalis, and sternocleidomastoid muscles. The mean AUC of the 8 patients who completed the study was significantly reduced from 404 to 196 and the product of pain duration and pain intensity was significantly reduced (12). Smuts and Barnard showed positive results in 30 of 50 patients treated with 100 U of Botox in an open and individual fashion (7, 13). Freund and Schwartz conducted a retrospective study of 21 patients with chronic tension-type headache (based on IHS criteria) who also had palpable muscle tenderness of the scalp or upper neck. Patients received botulinum toxin type A 100 U over five sites in the scalp and upper neck representing muscle points most tender to palpation. Eighteen patients experienced a >50% reduction in headache frequency, and 20 had a 50% reduction in tenderness to palpation. The investigators suggested that some chronic headaches may represent "variants of focal dystonias," accounting for the efficacy of botulinum toxin. Although the theory is intriguing, the results of this open-label study must be interpreted with caution (2, 14).

However, when randomized, double-blind, and placebo-controlled studies were performed with patients suffering from tension-type headache, contradictory results for the efficacy of botulinum toxin were found. Schmitt et al., studying 59 patients, could not find any significant difference between 20 U of Botox and placebo (15, 16). Burch et al. also could not show a significant difference in headache frequency between treatment with Botox (50 U) and placebo injected in pericranial muscles in 41 patients. However, there was a significant decrease of pain intensity in the treatment group with Botox compared with the control group (16, 17). Rollnik et al. studied the efficacy of 200 U of Botox A (presumably Dysport) against placebo. They treated 11 patients with 200 U of Dysport and 10 patients with placebo. After 4, 8, and 12 weeks, the 21 patients showed no difference (16, 18). Gobel et al. treated 10 patients each with either 80 U of Botox or placebo. In both cases, no reduction was found either in pain intensity, pain-free days or in use of analgesics (19).

In a study by Smuts et al., 37 patients with tension-type headache received Botox type A 100 U or placebo, divided among six injection sites: two in the temporal muscles and four in the cervical muscles. Patients kept a diary of headache intensity and frequency and medication use, starting 1 month before treatment and continuing for 3 months after injections were administered. The actively treated group showed a trend toward decreased headache severity over the 3 months after injection. This improvement reached statistical significance at month 3 relative to the pretreatment month. Similarly, the number of headache-free days was greater at month 3 than at baseline. The Chronic Pain Index, a subjective indicator of pain intensity, also reflected improvement in the actively treated patients but not in the placebo group. No serious adverse events were reported (20). Relja (21) reported on her data from a prospective, randomized, double-blinded 8-week crossover trial of Botox as a treatment for chronic tension-type headache in 16 patients who were resistant to medication. Patients received either Botox 35–80 U in saline vs. saline alone by multiple injections in the most tender pericranial muscles. No other medication was administered for at least 24 hours prior to either baseline measurements or Botox injections. Tenderness was assessed by palpation of frontalis, trapezius, and sternocleidomastoid muscles. Of the placebo patients, 94% still had moderate-to-severe headaches after treatment compared with only 25% (moderate only) in the Botox group (75% had no or mild headaches after treatment) (21, 22). Relja conducted another study (in 2001) in which 27 patients were randomized to placebo or the injection of 40–95 U of Botox every 3 months over a period of 10 months. The Botox group experienced a significant reduction of headache frequency and intensity compared with the placebo group (23). In a more recent study, Relja et al. (2004) conducted a prospective, double-blind, placebo-controlled crossover study with 16 patients and an open-label, long-term study with 30 patients. The results revealed that all the patients showed reduced severity of headache, reduced pericranial muscle tenderness and increased number of headache-free days during botulinum toxin A treatment. Moreover, a constant and cumulative trend of improvement was present, indicating better quality of life during botulinum toxin treatment (24). In the double-blind study, all outcome measures showed a significant difference between Botox and placebo treatments. Botox was significantly more potent in reducing muscle tenderness. Compared with placebo, patients treated with Botox showed significantly reduced maximum severity of headache. In the open-label study, there was a constant and cumulative trend of improvement in the number of headache-free days over the 18-month period. However, in most of these studies, the number of patients in the subgroups was too small.

In addition, the dose of botulinum toxin A and the injection sites were not always standardized. In some of these controlled studies, however (Gobel and Rollnik), there was a standardized design with defined injection sites rather than an individual selection of trigger points. Taking account of this point, Porta conducted a randomized comparative trial of tension-type headache treatment with botulinum toxin A and methylprednisolone injected into individual tender points in cranial muscles in 20 patients. A significant decrease in the median pain score at day 60 after injection of botulinum toxin A was found compared to methylprednisolone. All patients treated with botulinum toxin A experienced a gradual decrease in median pain severity scores at 30 days and 60 days after treatment. The beneficial effects of botulinum toxin A continued to increase 60 days after injection, whereas the effects of steroid therapy at this time point began to decline. Without a placebo group, however, it is not possible to assess the methodology or significance of this trial (25).

Thus, an important finding of experience to date with botulinum toxin A in therapy of tension-type headache is that the injection should be performed at the site of the pain or the trigger points, and not on a standardized basis. Just as the injection is made specifically into the affected muscle in the treatment of dystonia cases, this must also be done in the treatment of pain. It is essential that this crucial point be observed in future controlled studies and in open use. However, this point was contradicted in a study by Padberg et al. They conducted a randomized, placebo-controlled clinical trial to prove the efficacy of botulinum toxin for chronic tension-type headache. Patients were randomly assigned to receive botulinum toxin (maximum 100 U) or placebo (saline) in muscles with increased tenderness. After 12 weeks there was no significant difference between the two treatment groups in decrease of headache intensity on Visual Analog Scale (VAS), mean number of headache days, headache hours per day, days on which symptomatic treatment was taken, and number of analgesics taken per day. There was also no significant difference in patients' assessment of improvement after week 4, 8 and 12. Botulinum toxin was not proven effective in the treatment of chronic tension-type headache. Therefore, increased muscle tenderness might not be as important in the pathophysiology of chronic tension-type headache as believed (26).

Another factor to consider is the range of doses of botulinum toxin A used, which in the positive studies ranged from 15 – 100 U or 160 – 200 U of Dysport; the total dose injected would appear to be of secondary importance. Schulte-Mattler et al. (2004) conducted a follow-up study from their previous open-label study in 1999. This study was a prospective, multicenter, randomized, double-blind, placebo-controlled trial. Multiple pericranial muscles (frontalis, temporalis, sternocleidomastoid, auricularis, occipitalis, splenius capitus, semispinalis capitus, and trapezius) of 107 patients with chronic tension-type headache were treated either with 500 U of botulinum toxin (Dysport) or with placebo. The diagnosis was made strictly following the IHS criteria. Injections were made following a fixed scheme and not adjusted to the patient's symptoms. Patients kept a headache diary that was used to calculate the area under the curve at 6 weeks before and 12 weeks after the treatment as the main effect measure. Secondary effect measures were the number of days with headache, the number of days with intake of analgesics, the duration of nocturnal sleep, and the Beck Depression Inventory score. The results showed that there were no significant differences between the verum group and the placebo group in any of these variables. In addition, seven of the patients of the verum group had transient weakness of the eyelids, the neck, or both, indicating that a higher dose than used in this study does not seem sensible for the treatment of headache. The study significantly concluded that botulinum toxin A cannot be recommended for patients with chronic tension-type headache who do not sufficiently respond to the established therapeutic strategies (7).

It would also appear to be significant that a higher efficacy seems to result in cases where both migraine and tension-type headache exist. Most studies dealt with either one syndrome or the other (27). Klapper et al. treated patients with chronic daily headache in a double-blind, placebo-controlled trial using 25.5 – 72.5 U of Botox. In a subgroup with 2 injection regions they found a reduction in headache duration and in frequency of moderate and severe headaches (28). Wheeler achieved the same results in a group of 4 patients with chronic headaches associated with pericranial muscle tension, which had failed to respond to prolonged conventional treatment. The patients were injected in multiple sites with a total of 100 – 200 U of Botox. All of them had a significant reduction in headache severity and frequency with concomitant reduction in medication use for up to 8 months after treatment (29).

Additional studies of the prophylactic effect of botulinum toxin A on tension-type headache were either not controlled, had no exact diagnosis, had too few patients or did not define the reduction of headache frequency as the primary endpoint.

Klapper et al. enrolled 56 patients in their study. However, they separated them into four subgroups, and no exact headache diagnosis ("chronic headache") was given. Treatment with botulinum toxin A in both frontal and suboccipital sites caused a significant reduction of headache for one subgroup compared with the other three subgroups (28). The open study of Robbins with 79 patients treated with 24 U of Botox A had only "daily headache" as the diagnosis. After a control period of 3 months, 30% of the patients showed good or moderate improvement; 70% had no relief (30).

Rollnik et al., in another study, examined the efficacy of 500 U of botulinum toxin A (Dysport) in chronic tension-type headache and also studied the electromyography (EMG) activity of different face and neck muscles. The study was placebo controlled and parallel grouped (four patients in each group). Although the EMG activity was significantly reduced by botulinum toxin A, there was no effect on the headache (31).

Conclusion

Botulinum toxin A represents a completely new treatment option for patients with chronic pain syndromes, especially tension-type headaches. At this time, clinicians may consider botulinum toxin as a treatment for headache disorders in patients who cannot tolerate or do not benefit from standard therapies.

In our current review, the results were contradictory and inconclusive. In evaluating the open design studies, all but one seemed to show a favorable response to the treatment of tension type-headache with Botox. However, in the double-blind, placebo-controlled trials the results were contradictory for the efficacy of botulinum toxin. This may be due to the fact that varying doses of Botox were used. There were also differing injection sites: some researchers used individual injection sites or most tender muscles while in other studies there was a standardized injection design. In our own practice, patients receive a total of 100 units of Botox at standardized sites (suboccipital, frontalis, temporalis, and glabellar). Another aspect is the frequency of treatment. In the studies reviewed, it was shown that there was a cumulative effect with subsequent injections.

Therefore, further evidence is needed to determine whether this agent can serve as a first-line therapy for patients with less refractory headaches, and to determine optimal injection sites, doses, and frequency of treatment.

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THEME ISSUE

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Approach to Undifferentiated Chest Pain in the Emergency Department:

A Review of Recent Medical Literature and Published Practice Guidelines

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Abstract

Chest pain is the presenting complaint in over 6 million emergency department visits each year. Differentiating acute coronary syndrome (ACS) from other, noncardiac causes of chest pain is imperative in emergency practice. This article reviews the current medical evidence and published guidelines for the diagnosis of undifferentiated chest pain.

A MEDLINE database search was conducted for relevant English language articles discussing an approach to undifferentiated chest pain. The published guidelines of the American College of Emergency Physicians, the American Heart Association, and the American College of Cardiology were also reviewed.

The data surveyed suggest that, for all adult patients complaining of nontraumatic chest pain, a cardiac etiology for their presentation should be considered. History, physical examination, electrocardiogram, chest radiography, and to a lesser extent laboratory results can help differentiate ACS from other emergent diagnoses, e.g., aortic dissection, esophageal rupture, pulmonary embolus, pneumothorax, pneumonia, and pericarditis.

No single feature of a patient's history, physical examination, or diagnostic test results can diagnose ACS to the exclusion of other causes of chest pain. Consequently, patients presenting with a complaint of chest pain frequently require serial evaluations, and admission to an observation unit or the hospital.

Key Words: Angina pectoris, chest pain, differential diagnosis, electrocardiography, medical history taking, physical examination, practice guidelines, symptoms.

Introduction

THE COMPLAINT OF acute nontraumatic chest pain presents one of the most difficult diagnostic challenges in emergency medicine (EM). Patients with this chief complaint account for approximately 5% of all emergency department (ED) visits (1). Given that coronary artery disease is the leading cause of death in the United States (2), rapid identification of an acute myocardial infarction is the foremost consideration in the emergency physician's differential. Despite scientific advances in both understanding and detecting acute myocardial infarctions, an estimated 2.1–5.3% of patients presenting with an acute coronary syndrome (ACS) are sent home from the ED (3, 4).

Patients with ACS often have symptoms indistinct from those of other emergent conditions. Afferent somatic and visceral nerve fibers of the heart, lungs, aorta and esophagus all synapse at the same thoracic dorsal ganglia. Therefore, pain felt in any location from the jaw to the epigastrium can have origins in any of these anatomic structures. An apprehensive appearance and complaint of chest pain can be observed in patients with an aortic dissection, pulmonary embolism, pneumothorax, pericarditis or esophageal rupture. Delay in treatment and diagnosis of any of these conditions leads to an increase in morbidity and mortality. In addition, failure to diagnose myocardial infarction accounts for 25% of all malpractice dollars paid against emergency physicians (5). Yet an exhaustive cardiac work-up of patients with a psychiatric, gastrointestinal, or musculoskeletal cause of chest discomfort is both stressful to the individual and a drain on limited health care resources. The objective of this article is to review the current medical literature and practice guidelines recommendations with regard to the diagnosis of undifferentiated chest pain in the adult emergency department patient, to help determine which method or combination of methods may provide the quickest, most reliable differential diagnosis.

General Approach

Upon arrival in the ED, patients with abnormal vital signs and complaining of chest pain or who

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appear to be ill should be triaged to a critical care area. Intravenous access should be established and abnormalities in oxygen saturation treated with supplemental oxygen. To meet the goal of a less than 30-minute door-to-intervention time, all patients suspected of an acute myocardial ischemic event require a 12-lead electrocardiogram (ECG) obtained within 10 minutes of arrival in the emergency department. Furthermore, recently published ACC/AHA guidelines recommend 12-lead ECG performance by EMS personnel prior to arrival in the ED, if possible, to expedite care (6).

Key elements of the history consist of a description of the pain (quality, severity, duration, activity at onset, radiation, worsening and alleviating factors, and previous occurrence), pertinent medical conditions, medications, allergies, and treatment thus far. Initially, the skin and cardiopulmonary, vascular and neurological systems are briefly examined for pallor, diaphoresis, jugular venous distension, tracheal deviation, new murmurs, abnormal breath sounds, pulse and gross motor deficits. Together with the ECG and chest radiography, this approach can help distinguish an acute coronary syndrome from aortic dissection, pulmonary embolism, pneumothorax, pericarditis, or esophageal rupture. Further patient stabilization and treatment should occur in accord with a more detailed medical history and physical examination and in conjunction with laboratory testing and further diagnostic imaging. The physician should also remain aware of other (nonemergent) causes of non-cardiac chest discomfort. The basic data for differential diagnosis of the most common emergent and nonemergent causes of chest pain follow.

Emergent Causes of Chest Pain

Aortic dissection. More than 14,000 people die each year in the United States from aortic dissections (2). Most of these individuals are males (75%) in the seventh decade of life (7). A tear in the intimal layer of the thoracic or abdominal aortic wall can result from either longstanding hypertension or a structural abnormality. Stanford Type A dissections involve the ascending aorta with or without involvement of the descending portion. Stanford Type B dissections are located in the descending aorta beyond the junction with the subclavian artery. Type A dissections are usually treated surgically and Type B with medical control of blood pressure. Risk factors for this disease include arteriosclerosis, advanced age, Marfan's syndrome, connective tissue disease, Turner's syndrome, and hypertension (7–10). Elevated blood pressure may drive the initial tear to expand into a false lumen. Impending rupture leads to a myria of symptoms and signs in the supplied organs brain, heart, kidneys and intestines. The medica literature abounds with atypical cases of aortic dissections presenting as a stroke, syncope, congestive heart failure, isolated limb ischemia or numbness, abdominal discomfort, flank pain, acute rena failure or gastrointestinal bleeding.

A patient who complains of chest pain that i maximal at onset with an accompanying neurological or pulse deficit should immediately be suspected of having an aortic dissection. Failure t take an adequate pain history on initial clinica evaluation has been found to delay diagnosis (10) A 2002 review of 274 MEDLINE articles found history of sudden pain with a maximal intensity a onset to have a pooled sensitivity of 90% in detecting thoracic aortic dissection (9). The pain i frequently described as "tearing" or "ripping," with radiation to the back, interscapular, or abdominal region. Physical examination may revea jugular venous distension from cardiac tamponade blood pressure differential of greater than 20 mn Hg between extremities, mediastinal air or aorti regurgitation. Classic findings such as pulse quality difference between limbs (15–38%) (7, 11) an gross motor defect (17%) occur more commonly i Type A dissections. Their presence increases th positive likelihood of disease, from 5.7 for a puls or blood pressure differential to 6.6–30 with neurological deficit (7). Chest radiography usuall reveals a widened mediastinum, loss of the aorti contour, displacement of the aorta, or pleural effusion. Since as many as 10% of patients will have normal initial radiograph, this radiograph canno be used to exclude disease (7). ECG findings ca show left ventricular hypertrophy of longstandin hypertension or, for dissections occurring retrograde into the coronary arteries, an acute myocardial infarction.

Clinicians must quickly distinguish aortic dissection from an ACS before the administration o antiplatelets and antithrombin agents. No singl finding is sufficient to exclude the diagnosis o aortic dissection, but a constellation of clinica variables (immediate, maximal tearing or rippin pain; pulse or blood pressure differential; mediastinal widening) can identify up to 96% of case (11). Patients thus identified will require medica control of hypertension, surgical consultation, an further imaging, e.g., transesophageal echocardiography, computed tomography, magnetic resonance imaging. Overall in-hospital mortality fo aortic dissection, from the International Registr of Acute Aortic Dissection (IRAD), is reported a 27% (7).

Pulmonary embolism. Pulmonary embolism (PE) represents a common, life-threatening and frequently missed diagnosis in the ED. An estimated 187,000 cases of first-time venous thromboembolism occur in American adults over the age of 45 years (12). These patients can present with chest pain of pleuritic nature, fatigue, dyspnea, syncope, hemoptysis and/or cardiac arrest (13, 14). Risk factors for PE include increasing age, immobilization, recent surgery, malignancy, pregnancy, trauma, and previous thromboembolic disease (12, 14, 15). Physical findings on examination can be minimal. Normal oxygen saturation or presence of a fever cannot exclude the diagnosis (14, 16, 17). Increased respiratory rate is the most common sign associated with PE (14, 17). An electrocardiogram can show acute pulmonary hypertension and a right heart strain pattern, or T wave inversions (17). Chest radiography may reveal atelectasis, pulmonary parenchymal disease or pleural effusions, or it may be entirely normal (14, 17). Patients should be stratified into low, intermediate and high-risk categories (18) (see article on "Pulmonary Embolism" in this issue of the *Journal*). The advent of rapid, enzyme-linked immunosorbent assay (ELISA)-based d-dimer testing has proven useful in excluding the presence of PE in low-risk patients (19–21).

Esophageal perforation. Spontaneous esophageal rupture (Boerhaave's syndrome) is a rare but potentially lethal cause of chest pain. As with aortic dissection, if this condition is misdiagnosed as ACS, the unintentional administration of thrombolytics may lead to rapid clinical deterioration (22). Given its relative rarity, there are no well-designed studies to help guide evidence-based decision making regarding the diagnosis and management of the condition. A classic history of vomiting followed by severe chest pain, shortness of breath, subcutaneous emphysema and rapid circulatory collapse is not always present. Median age of occurrence is from 63–71 years (23, 24), with isolated cases reported in younger adults (25). Depending on the case series, 12–50% of patients have no history of prior vomiting (23, 24, 26). Patients with esophageal perforation generally appear ill and may complain of dyspnea, cough, fever and abdominal pain. Patients presenting more than 12 hours after the onset of symptoms may show signs of sepsis (26). Physical examination may reveal diminished breath sounds, heart sounds with audible crepitus (Hamman's crunch), or subcutaneous air in thorax or neck. The majority of patients (71–100%) will have abnormalities on chest radiography that include pneumomediastinum, hydro-pneumothorax, pleural effusion or mediastinal widening (23, 24, 27). Confirmatory studies include esophageal contrast radiography, computed tomography (CT) scans, or endoscopy. Studies present mortality rates varying from 14–64% (23, 24, 26, 28); they are higher with a delay in diagnosis beyond 24 hours. All ill-appearing patients with undifferentiated chest pain should be questioned about antecedent vomiting and have their chest radiographs reviewed before medical treatment is initiated.

Pneumothorax. Patients with a spontaneous pneumothorax generally present with pain and complaints of shortness of breath. Risk factors for occurrence include smoking, previous pneumothorax, chronic obstructive pulmonary disease, underlying pulmonary pathologies, and abrupt changes in barometric pressure. Pain is described as sudden, sharp and pleuritic in nature. Associated respiratory distress can be severe. If a tension pneumothorax develops, the trachea may be deviated away from the collapsed lung, and jugular venous distension may be present. Absence of breath sounds and hyper-resonance to percussion may be seen on the effected side. An upright chest radiograph is typically diagnostic. According to an American College of Chest Physicians (ACCP) consensus statement, patients with small, non-expanding pneumothoraces can be safely discharged from the ED after 6 hours of observation with follow-up in two days (29). Patients with large pneumothoraces or unstable vital signs require placement of a chest tube and hospital admission.

Acute pericarditis. Approximately 800 deaths per year in the United States are attributed to diseases of the pericardium and myocardium (2). In a majority of patients, acute pericarditis is of either viral or idiopathic etiology (30–32). More than half of the patients will present complaining of chest pain (31, 33) that may radiate to the back, neck or shoulders. In contrast to acute coronary syndromes, pericardial pain worsens with inspiration and is improved while sitting up and leaning forward. Approximately 25–40% of patients will complain of dyspnea and 17% of fever (31, 33). At some point during their disease, 85% of patients without a severe pericardial effusion will have a pericardial friction rub (32). Individuals with associated cardiac tamponade may show jugular venous distension, tachycardia, hypotension, and/or pulsus paradoxus. Published guidelines of the European Society of Cardiology (ESC) suggest an ECG, chest radiography, laboratory testing (ESR, C-reactive protein, lactic dehydrogenase [LDH], WBC, cardiac markers) and echocardiography, with Level B evidence for the diagnostic pathway (34). Classical ECG findings include concave ST segment elevation, T-wave inversions, and PR-segment depression. ECG changes occur throughout the precordium and, unlike ACS, are not distributed in distinct anatomic regions. Low QRS voltage throughout the limbs leads is suggestive of cardiac tamponade (35). A chest radiograph may demonstrate an enlarged cardiac silhouette or be entirely normal. ED ultrasonography has emerged as the preferred diagnostic test in these cases. Younger patients and those with recent infection may have elevations of troponin I, unrelated to symptom intensity or disease severity (30, 36). Management consists of pericardiocentesis for severe cardiac tamponade, treatment of the underlying cause, and nonsteroidal anti-inflammatory drug administration.

Pneumonia. Pneumonia is a potentially life-threatening condition in the immunocompromised elderly or in individuals with significant co-morbidities. Approximately 65,000 people in the United States die each year from pneumonia (2). Patients may complain of chest pain that ranges from sharp and pleuritic to dull and substernal. Physical examination may reveal fever, rales, decreased breath sounds or bronchial breath sounds and varying degrees of respiratory distress. Elderly patients notoriously present with few symptoms or signs and may have only an alteration in mental status. Diagnosis is usually confirmed on chest radiograph, with few cases requiring a computed axial tomography (CAT) scan or bronchoscopy. Decisions to admit or discharge should be based on risk stratification via published guidelines or the pneumonia severity index (37, 38). Antibiotic selection is based on the patient and local bacterial sensitivities to various drugs (39, 40). Clinicians should be aware of reports of increasing resistance of pneumococcal pneumonia to fluoroquinolones (41, 42). One recent retrospective review of 18,209 patients found antibiotic administration within 4 hours of hospital arrival to be associated with a decrease in in-hospital mortality [adjusted odds-ratio = 0.85 (CI 0.74–0.98)] and 30-day mortality [AOR 0.85 (CI 0.76–0.95)] (43, 44).

Acute coronary syndrome. Acute coronary syndromes can be divided into ST-segment elevation acute myocardial infarction (STEMI), non-ST segment elevation acute myocardial infarction (NSTEMI) and unstable angina (UA). All three have similar clinical features and are difficult to distinguish from other cases of chest pain. A standard 12 lead electrocardiogram is the most valuable tool in the investigative armamentarium (45). Chest radiography is useful in excluding other disease process and assessing for the presence of congestive heart failure. Cardiac biomarkers are important in distinguishing between the three entitie and form the basis of the new definition of acut myocardial infarction. ACS is discussed in detai in other articles in this issue of the *Journal*.

Nonemergent Causes of Chest Pain

Panic disorder. Anxiety disorders and isolate panic attacks occur in 2–13% of the adult population (46, 47). As per the Diagnostic and Statistica Manual of Mental Disorders, 4th edition (DSM-IV definition, attacks are accompanied by any four o the following symptoms: palpitations, diaphoresis tremor, dyspnea, choking, chest pain or discomfort nausea, dizziness, derealization or depersonalization, fear of losing control or dying, paresthesias chills or hot flushes (48). An estimated one millio panic disorder patients present to EDs each yea with complaints of chest pain (49, 50). The vast majority of these patients (98%) are discharged without a definitive diagnosis of their condition (49) Recently published studies have found a correlatio between panic disorder and lack of pre-existin coronary artery disease (CAD), atypical quality t the pain, female sex, younger age, and a high self reported anxiety level (51–53). However, pani disorder and CAD frequently co-exist, which ca lead to exacerbation of both disease states. Som success has been reported in both screening fo panic disorder and starting anxiety medications i the ED chest pain unit (54).

Gastrointestinal diseases. Several disorder of the gastrointestinal tract, including gastroesophageal reflux, esophageal spasm, peptic ulcers pancreatitis, biliary colic and cholangitis, can al present with chest pain. Indeed, up to 40% of ches pain patients seen in the ED and not diagnose with ACS may have gastroesophageal disease (55) Discriminating these disorders from ACS can b difficult based solely on history and physical examination. Pitfalls abound, from early closure o diagnoses to missing concomitant presentations Chest pain from gastroesophageal reflux (GERD is usually described as a burning in the mid-epigastrium or in the lower chest. However, chest pai described as being of this nature does not exclud the presence of cardiac ischemia (56, 57).

Moreover, given the prevalence of GERD i the adult population, previous history of the disease does not exclude an ACS event. Gastroesophageal reflux may provoke myocardial ischemia in patients with underlying coronary arter disease (58). Diagnosing GERD in chest pain patients by antacid administration is not acceptabl medical practice. Similarly, esophageal spasm pai and other non-cardiac disorders can improve wit

Key Concepts

1. Undiagnosed myocardial infarction is a major cause of morbidity and mortality for chest pain patients.
2. History, physical examination and chest radiography are often useful in identifying non-ACS etiologies of chest pain.
3. Aortic dissection and acute myocardial infarction can coexist in the same patient.
4. A significant percentage (25%) of patients with acute coronary syndrome (ACS) do not have a primary complaint of chest pain
5. Gastroesophageal symptoms are non-specific for gastrointestinal etiology and can be seen in ACS.

nitroglycerin administration (59). Peptic ulcer disease can wake individuals from sleep and is usually located in the mid-epigastrium. A perforated duodenal ulcer can present with severe chest pain, vital sign abnormalities, and free air on upright chest radiography. Diagnoses of acute pancreatitis and biliary tract disease can be achieved from history, physical examination, bedside ultrasonography and supporting laboratory studies. Patients presenting with acute chest pain suspected of having a gastrointestinal etiology should nonetheless have their cardiac risk factors assessed and ACS considered in the differential diagnosis.

Chest wall syndromes and nerve root compression. Approximately 28% of undifferentiated non-cardiac chest pain patients may have chest-wall syndromes (55). Costochondritis is an inflammation of the costal cartilages that can result in an acute, well-localized, sharp chest pain. Patients, who appear otherwise well, may feel increased discomfort with deep respiration or movement. Pain is reproducible upon palpation of the involved cartilage. Pain that is positional, pleuritic, or reproduced with palpation gives a likelihood ratio of 0.2–0.3 for myocardial infarction (60). Interpretation of this finding should be balanced with the overall clinical picture, for patients with an ACS event can have a tender chest wall.

Compression of the cervical or thoracic ventral nerve roots can produce a dull chest pain that mimics angina. The discomfort is worsened with neck movement, coughing, or sneezing. On physical examination, application of steady pressure to the head increases axial loading on the nerve root, which can reproduce symptoms (Spurling's maneuver). Further diagnostic testing in the absence of other neurological findings is not indicated in the emergency department setting. Patients can be safely discharged with follow-up arrangements.

Conclusions

Adult patients presenting to the emergency department with a chief complaint of chest pain can have a myriad of conditions. Emergent conditions such as aortic dissection, pulmonary embolism, pneumothorax, pericarditis, esophageal rupture and ACS require rapid diagnosis and treatment. Once the patient is stabilized, other diagnoses, such as anxiety disorder, gastritis, gall bladder disease, and muscle-skeletal pain can be considered. An individual may have more than one cause for a clinical presentation. In the evaluation of patients with acute chest pain, it is critical that all potential causes be considered and premature closure of the diagnosis be avoided.

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Acute Decompensated Heart Failure:

Formulating an Evidence-Based Approach to Diagnosis and Treatment (Part I)

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Abstract

Heart failure is a disease that affects approximately 5 million Americans, accounts for 1 million hospitalizations annually, and represents the most common hospital discharge diagnosis for patients over the age of 65. Despite the significant impact of this disease, the accepted approach to treatment of acute decompensated heart failure (ADHF) has changed little in over 40 years. Another potential problem is that differentiating ADHF from other causes of dyspnea can be difficult, as historical elements, physical examination findings, and radiographic results lack adequate sensitivities to accurately identify the disease. This article, the first of a two-part series, will explore the historically accepted disease models for heart failure and their relevance to developing a therapeutic approach to ADHF. Additionally, diagnostic issues in heart failure will be examined, particularly the emerging role of natriuretic peptide assays for the identification of ADHF.

Key Words: Acute decompensated heart failure, natriuretic peptides, vasodilator response, neurohormones.

Introduction / Epidemiology

Heart failure is a widespread disease. An estimated 5 million Americans suffer from heart failure, with over 500,000 new cases diagnosed annually (1, 2). The disease accounts for approximately 1 million hospitalizations annually and represents the most common discharge diagnosis for patients over the age of 65 (1). The financial burden that heart failure places on our health care system is enormous. It represents Medicare's single largest expense, with direct costs estimated at $25.3 billion in 2005 (3). By comparison, the combined direct cost of all cancers in the US was $69 billion in 2004 , and HIV cost an estimated $13.6 billion in 1999 (3). In spite of advances in therapy, the diagnosis of heart failure carries an abysmal prognosis. In one study of over 30,000 patients admitted with new onset heart failure, the 30-day and one-year mortality rates were an astounding 12% and 30%, respectively (4). Of concern for the future, the hospitalization rate for heart failure has increased 159% in the past 10 years (1). Given our success in treating cardiac ischemic disease and our aging national population, the incidence of the disease can be expected to continue to increase in the coming decades.

Despite the enormous impact of heart failure and significant changes in our understanding of the physiology of the disease, the therapeutic approach to acute decompensated heart failure (ADHF) has changed little in the past 40 years. Registry data demonstrate that for a majority of patients hospitalized for heart failure, the only intravenous medication they will receive is a diuretic (5). The static nature of this therapeutic approach, largely unchanged in over 4 decades, is undoubtedly a result of multiple factors that influence clinical decision making in ADHF, including: few randomized controlled trials on which to base treatment decisions, a lack of consensus guidelines from professional organizations, and an apparent underappreciation of disease severity. The last point is underscored by the fact that despite an in-hospital mortality rate

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Glossary

ACE = angiotensin-converting enzyme
ADHF = acute decompensated heart failure
ANP = atrial natriuretic peptide
BNP = b-type natriuretic peptide
CHF = congestive heart failure
COPD = chronic obstructive lung disease
CNP = c-type natriuretic peptide
ECG = electrocardiogram
ED = emergency department
EDTA = ethylenediaminetetraacetic acid
JVD = jugular venous distension
LV = left ventricular
MR = mitral regurgitation
NT-ANP = N-terminal ANP
NT-BNP = N-terminal BNP

that is similar to that of non-ST-elevation myocardial infarction, the vast majority of patients hospitalized with ADHF receive relatively non-aggressive medical care (6–8).

Pathophysiology—Choosing the Right Disease Model

Our clinical approach to ADHF is a reflection of the conceptual model we choose to apply to the disease. Disease models are essential to the practice of medicine. From a research perspective, a conceptual model allows us to form the hypotheses that clinical trials are designed to test. From a clinical perspective, our understanding of a disease model always influences our therapeutic approach to that disease. As evidence accumulates, models change, which in turn leads to changes in the diagnostic and treatment process.

As an example, the evolution of treatment guidelines for myocardial infarction from an approach that favored bed-rest and nitrates 50 years ago, to the anti-platelet and anti-thrombin treatment regimens of today, is a reflection of changes in our conceptual model of cardiac ischemia. Similarly, we would expect the therapeutic approach to ADHF to mirror changes to the accepted model of the disease. Interestingly, this does not appear to have occurred. A brief discussion of the evolution of the conceptual model for heart failure is important, because it not only helps explain why prevailing practice patterns exist, but also helps identify opportunities to improve our care of heart failure patients.

Three distinct heart failure models have existed over the past 50 years (9). Though these models have been used primarily to understand chronic heart failure, they offer valuable insight into how we should approach periods of acute decompensation. Each begins with the premise that an index event (myocardial infarct, chronic hypertension, myocarditis, etc.) leads to a decline in cardiac function. The end result of this process, including compensatory responses and therefore the ideal approach to treatment, varies with each model and will be described below.

The Cardiorenal Model

The cardiorenal model, first described in the 1940s, viewed heart failure as an acute process defined by the presence or absence of edema as a result of decreased renal blood flow secondary to cardiac dysfunction (9). As volume retention and contractility were believed to be the primary determinants of decompensation, treatment centered on volume reduction with diuretics and contractility support with digoxin. No controlled studies were done to assess the efficacy of this approach, and by the 1970s the validity of the cardiorenal model had come into question for several reasons. First, the model could not explain the progressive nature of the disease (9). Second, invasive hemodynamic monitoring in heart failure patients consistently demonstrated excessive peripheral vasoconstriction, which was found to contribute significantly to decreases in cardiac performance (10).

However, even though the cardiorenal model was largely abandoned as an acceptable model for heart failure over three decades ago, our current approach to ADHF still appears to be based on it. As previously noted, the only parenteral medication most heart failure patients receive during hospitalization is a diuretic (5). Targeting volume reduction as the primary goal of initial therapy makes intuitive sense only if we accept the premise that volume overload is the most important physiologic abnormality in ADHF. In fact, the central issue in heart failure is a decline in cardiac performance. Fluid retention develops as a compensatory response to that primary deficit and is only one part of the clinical picture of heart failure. While it is true that diuresis eventually improves cardiac function as volume status returns to baseline, diuretics alone have no direct beneficial effect on cardiac performance. In fact, because they can cause a reflexive increase in sympathetic tone and serum renin activity, the initial response to diuretic therapy may be a transient worsening of ventricular output (11). Increasingly, there is data to suggest that an approach that emphasizes diuresis as the mainstay of initial therapy has potential shortcomings, the evidence of which will be more thoroughly explored in Part II of this article.

The Cardiocirculatory Model

The extreme peripheral vasoconstriction that is typical of heart failure significantly impacts cardiac performance, a concept first described in the 1970s as the cardiocirculatory model of heart failure (9). Venous constriction, leading to an increase in preload and ventricular wall stress, and arterial constriction, causing an increase in afterload, both combine to cause a decrease in cardiac output, which results in decreased renal perfusion, leading eventually to sodium retention and volume overload (9). This sequence of events, initially characterized as the cardiocirculatory model, presents heart failure as a derangement between the heart and circulatory system, suggesting that the focus of therapy should be shifted away from the kidney to the peripheral blood vessels, and the of vasodilator agents. The use of vasodilator therapy in ADHF has been shown to have both short- and long-term benefits. These benefits are presumably a result of the so called "vasodilator response" and reflect changes in cardiac loading conditions that result in improvement of cardiac performance (12).

The vasodilator response. The potential benefits of the vasodilator response, reflective of accepted basic cardiac physiology, are listed in Table 1. Ventricular force of contraction and therefore cardiac output are partially dependent on sarcomere stretch, a result of end-diastolic volume (preload) (13). Generally, increasing preload increases the overlap between actin and myosin filaments in the sarcomere, which results in an increase in ventricular force of contraction (Frank-Starling relationship). During periods of volume overload, significant increases in preload result in overstretching of the sarcomere, leading to a decline in the force of contraction because of less overlap between actin and myosin filaments. In this setting, decreasing preload allows for shortening of the sarcomere, more overlap of actin and myosin filaments, and a greater contractile force, with a subsequent improvement in cardiac output.

Additionally, in the presence of systolic dysfunction, changes in afterload have a significant effect on cardiac output (13). As a result, decreasing afterload with arterial vasodilation results in improved ventricular performance.

TABLE 1
Vasodilator Response

1. Venous dilation / decreased preload
   ↓ Ventricular wall stress
      ↑ actin/ myosin overlap = ↑ force of contraction
   ↓ Ventricular dilatation
      ↓ 2° mitral regurgitation

2. Arterial dilation / decreased afterload
   ↓ Outflow resistance
      improved cardiac output
      ↓ 2° mitral regurgitation

3. Combination of decreased preload / afterload
   ↓ filling pressures
      ↓ pulmonary edema / dyspnea
   ↑ cardiac output
      improve renal perfusion / diuresis

Finally, secondary mitral regurgitation (MR) is a common contributor to decreased cardiac output in ADHF. "Secondary MR" refers to valvular incompetence that develops as a result of structural changes that accompany ventricular dilation during periods of volume overload. The incidence of secondary MR in ADHF approaches 100% in some studies (14). Significantly, in patients with secondary MR, treatment with an IV vasodilator has been shown to increase forward stroke volume by 40–60% and decrease regurgitant volume by 44% (15, 16).

In summary, the vasodilator response, by altering loading conditions in the heart, provides mechanism to dramatically improve cardiac performance during periods of decompensation.

The Neurohormonal Model

Because vasodilatory efficacy was neve clearly linked to long-term mortality and the cardiocirculatory model did not offer an explanatio for disease progression, the search for a unifyin model for heart failure continued (10). Early wor on the neurohormonal model in the 1990s developed as a result of observations that certain biologically active molecules were present in increased amounts in heart failure patients (11) These molecules, initially termed "neurohormones," were found to have significant effects o cardiac performance, vascular tone, and intravascular volume, and in essence provided an explanation for the hemodynamic abnormalities commo to heart failure patients. Although their expressio is initially a compensatory mechanism to a fall i cardiac output, chronic overexpression of these molecules was found to contribute to disease progression and episodes of decompensation via several mechanisms. The most well established neurohormonal systems are listed in Table 2.

Physiologic effects of neurohormonal activation. As a syndrome, heart failure patients share three common physiologic abnormalities: a decline in cardiac performance (related to either systolic or diastolic dysfunction), an increase in vascular tone, and varying degrees of volume retention. Neurohormonal pathways have significant influence over each of these physiologic parameters (Table 2).

One of the body's first responses to a decline in cardiac output is a reflex increase in sympathetic tone, which increases heart rate and contractility via beta-receptor stimulation. This response initially allows for maintenance of cardiac output, but with chronic stimulation, "downregulation" of beta receptors occurs, eventually leading to a decrease in inotropic response (17). In addition, endothelin, produced in both the vascular endothelium and ventricular tissue, has been shown to have negative inotropic effects in the failing heart (18). Serum norepinephrine, angiotensin, vasopressin, and endothelin all have well-described vasoconstrictive properties. Neurohormonal activation results in an overexpression of each of these peptides, a reasonable explanation for the increase in vascular tone common to the syndrome of heart failure (11, 19, 20). Finally, neurohormonal pathways, via aldosterone and vasopressin (anti-diuretic hormone), directly result in volume retention (20–22).

Perhaps the most appealing feature of the neurohormonal model is its ability to explain the progressive nature of heart failure as a disease process. Even when identifiable variables are controlled (e.g., ongoing cardiac ischemia, dietary indiscretion, and medication noncompliance) heart failure is a progressive disease. Disease progression, reflected by worsening ventricular function, is believed to occur as a result of cardiac remodeling, in which changes occur at the cellular level of the heart, including myocyte hypertrophy, cellular apoptosis, and fibroblast proliferation and fibrosis. Essentially, healthy ventricular myocardium that is compliant and fills easily with blood during diastole, and pumps well during systole, is replaced by stiff, fibrotic tissue that neither fills nor pumps well. As a result, ventricular function progressively worsens, and the clinical syndrome of heart failure becomes apparent. In both human and animal models, neurohormonal activation has been shown to directly promote cardiac remodeling via its toxic effects on myocardial tissue (23–25).

TABLE 2
Neurohormonal Activation in Heart Failure

Neurohormonal System	Physiologic Effects
Sympathetic nervous system	PV, VR
Renin angiotensin aldosterone system	PV, FR, VR
Endothelin system	PV, VR, NI
Antidiuretic hormone (vasopressin)	PV, FR, VR
Natriuretic peptides	vasodilation, diuresis

PV = peripheral vasoconstriction, VR= ventricular remodeling, FR= fluid retention, NI = negative inotrope

The importance of neurohormonal activation in heart failure is underscored by its clear link to short- and long-term outcomes. Serum norepinephrine, endothelin, and renin levels have all been strongly linked to mortality, as has hyponatremia, a reflection of vasopressin activity (26–28). Furthermore, every medication that has been shown to decrease mortality in heart failure attenuates neurohormonal activity: beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and spironolactone (an aldosterone antagonist) all exhibit significant effects on neurohormonal pathways, and presumably this is the mechanism of their benefit (29–31).

Although the importance of neurohormonal activation in the development and progression of heart failure appears clear, its direct importance in ADHF has been less studied. Given the fact that neurohormonal activation is directly responsible for the physiologic derangements common to ADHF, it seems intuitive that neurohormonal blockade would help speed return to a compensated state. Additionally, since the expression of neurohormones is increased during periods of decompensation, and these molecules are known to promote cardiac remodeling, the question arises as to whether remodeling accelerates in this setting. If true, therapy that provides neurohormonal blockade in ADHF may help slow overall disease progression, a consideration that will become increasingly important in the future, since many of the heart failure medications currently being developed selectively target neurohormonal pathways.

Also, relevant to this discussion is the role of the natriuretic peptides in heart failure. Natriuretic peptides are a group of endogenously occurring proteins that are released in response to ventricular stretch (32). The release of atrial natriuretic peptide (ANP, synthesized primarily in the atria), and b-type natriuretic peptide (BNP, synthesized in the ventricles) is increased in heart failure (33). Both ANP and BNP have diuretic, natriuretic, and vasodilatory effects and act in a compensatory manner upon the physiologic derangements present in heart failure (34, 35). Additionally, they inhibit aldosterone secretion in the adrenal cortex, renin secretion in the kidney, and endothelin and sympathetic activity (36–38). Because they attenuate neurohormonal activity, natriuretic peptides offer a potentially protective mechanism against pathologic cardiac remodeling in heart failure.

Although levels of ANP and BNP increase in heart failure, their physiologic effect in this setting is blunted, possibly as a result of down-regulation of peptide receptors. Since they are overexpressed during periods of decompensation, natriuretic peptides have additional utility as diagnostic markers of myocardial dysfunction and heart failure.

Choosing the Right Disease Model

Because the evidence regarding the ideal treatment approach to ADHF is limited, formulating a therapeutic approach based on an acceptable disease model makes intuitive sense. Each model described above offers legitimate, if incomplete, insight into the physiology of decompensated heart failure, suggesting that a combined approach may be appropriate.

The vast majority of patients presenting with ADHF do so because of dyspnea, a result of fluid redistribution to the lungs reflective of cardiac dysfunction, specifically an increase in ventricular filling pressures. Since resolution of symptoms and return to a compensated state depends on normalization of filling pressures, this appears to be the most logical target for initial therapy. From this perspective, an emphasis on diuresis as the mainstay of therapy, as directed by the cardiorenal model, provides at best an inefficient, and at worst an ineffective mechanism for treatment. In contrast, an approach that focuses on reduction of filling pressures via the vasodilator response provides a direct mechanism to rapidly improve cardiac loading conditions, thereby increasing cardiac output. Furthermore, increasing cardiac output improves end organ perfusion including renal blood flow, presumably allowing for more effective subsequent diuresis. Finally, since neurohormonal pathways are directly responsible for the hemodynamic abnormalities that define decompensated heart failure, medication classes that provide direct neurohormonal blockade presumably offer superior efficacy for the treatment of ADHF. This knowledge should be incorporated into the design of any therapeutic approach.

Diagnostic Options in Acute Decompensated Heart Failure

Conventionally, the initial diagnosis of ADHF is made based on the patient's history and physical exam, with additional information provided by a chest radiograph and electrocardiogram (ECG). The diagnosis, once suspected, is later confirmed by cardiac catheterization, echocardiogram, or radionuclide studies. Unfortunately, clinical findings tend to be neither sensitive nor specific for the diagnosis of heart failure (39–42). For example, jugular venous distension (JVD) has a specificity of 90% but a sensitivity of only 30%. Also, because the correct measurement is highly dependent upon the practitioner, the reproducibility of JVD is low (43). An S3 gallop, representative of rapid ventricular filling, is a highly specific but insensitive indicator of heart failure and can be particularly difficult to identify in a noisy emergency department (ED) setting (41). Other physical findings, such as pulmonary crackles or effusion, wheezing, and pedal edema, also carry a low combination of sensitivity and specificity, so that isolated findings alone are not very helpful in identifying the presence or absence of disease (44).

Chest radiography has long been considered a useful modality for diagnosing ADHF. When visualized, redistribution of pulmonary blood flow and pulmonary edema are accurate indicators of increased pulmonary artery wedge pressures characteristic of ADHF (44). Several studies, however, demonstrate the diagnostic limitations of chest radiography. In one small study of 22 subjects, Mahdyoon et al. demonstrated that patients with end-stage heart failure may have only cardiac enlargement without any evidence of radiographic pulmonary congestion, despite a significant increase in pulmonary artery wedge pressure (45). In another review of 880 patients presenting to the ED with dyspnea, radiographic evidence of ADHF (cephalization or pulmonary edema) had a specificity of 96–99% but a sensitivity of only 6–41% (44). Clearly, while radiographic findings of heart failure are quite helpful in identifying the disease, their absence does not preclude the diagnosis of ADHF.

Several ECG findings, including left bundle branch block and left ventricular hypertrophy, increase the likelihood of systolic dysfunction and therefore may have utility in identifying patients with ADHF. A recent study of 128 patients referred for evaluation of possible heart failure found that

QRS duration was an independent predictor of left ventricular dysfunction (EF<50%) (46). A prolonged QRS of either > 0.11 s or > 0.12 s had a specificity and positive predictive value of 90% and 98%, respectively. Sensitivities, however, were significantly lower (75–81%).

Recognizing that commonly available information concerning individual alternatives lacks the sensitivity or specificity to accurately diagnose ADHF, many investigators have examined a combined approach to the diagnosis. For example, the Framingham, Boston, and Duke criteria require multiple data elements (47, 48). Yet none of these criteria have shown adequate sensitivities or specificities to accurately diagnose ADHF.

The need for a simple, objective test to identify ADHF has driven much of the recent interest in the utility of the natriuretic peptides as an indicator of acute decompensation (49–51). In response to myocardial stretch, natriuretic peptides are synthesized as preprohormones, which after being processed to prohormones, are split into an inactive N-terminal fragment (NT- proANP or NT-proBNP) and a biologically active peptide (ANP and BNP), either of which may be measured as an indicator of heart failure (52).

Although all three natriuretic peptides (ANP, BNP, and c-type natriuretic peptide [CNP]) have been studied as markers of ventricular dysfunction, BNP testing is generally the most readily available in the ED setting and appears to be the most useful in identifying ADHF. The utility of BNP to identify ADHF was first studied in 1994 with 52 patients hospitalized for evaluation of acute dyspnea (49). In this study, radionuclide ventriculography and pulmonary function test were performed on each patient, and a panel of cardiologists, blinded to BNP results, determined the final diagnosis. BNP was found to have a sensitivity of 93% and a specificity of 90% for the diagnosis of heart failure.

More recently, point-of-care BNP testing has been evaluated in multiple studies in the ED setting. An early pilot study, observing 250 patients presenting with dyspnea to a Veteran Administration Hospital, found that with a BNP cutoff of 80 pg/mL, the sensitivity and negative predictive value for ADHF was 98% while the specificity was 92% (50). The sensitivity and specificity demonstrated in this study, higher than previously reported, may have been related to the fact that the study included only men and the mean age (64 years) was somewhat younger than would be expected in the general heart failure population. As BNP levels are known to increase with age and are typically higher in women than men, these results may not be applicable to the general population (52).

To address this issue, the Breathing Not Properly multinational study evaluated 1,586 patients who presented to seven emergency departments with acute dyspnea (51). A BNP level was measured for each patient at the time of presentation, and ED physicians, blinded to the result of the BNP assay, assessed the likelihood of congestive heart failure being the cause of the patients' acute dyspnea. Subsequently, two cardiologists reviewed the medical records of each patient, including the official interpretation of the ED chest X-ray, medical records that were not available at the time of presentation, follow-up tests such as echocardiogram, radionuclide angiography or left ventriculography, and the hospital course, to confirm the ED diagnosis.

The results of this study suggest that when compared to other clinical features, a BNP level is the most accurate predictor of the presence or absence of ADHF, with a sensitivity of 90% at a cutoff value of 100 pg/mL. As an isolated test, BNP was found to more accurately diagnose ADHF (83%) than either the National Health and Nutrition Examination Survey criteria (67%) or the Framingham criteria (73%) (51). Among patients for whom the clinician was highly confident of the diagnosis of ADHF, the use of BNP levels in this study raised the diagnostic accuracy by 10%. Perhaps more important, in the one-third of patients whose diagnoses were uncertain, based on clinical findings, adding a BNP level correctly identified 74% with ADHF and reduced the number of false negative diagnoses (for ADHF) to 7% (51).

Although these results appear very encouraging, the limitations of the BNP assay as a diagnostic aid for clinicians should be noted. A systematic review of the six ED-based BNP studies published through 2003 resulted in the following recommendations (53). BNP levels less than 50–80 pg/mL essentially rule out ADHF, while levels between 400 and 1,000 pg/mL and greater than 1,000 pg/mL are moderately and highly predictive of ADHF, respectively; BNP levels between 80 and 400 pg/mL represent a so-called diagnostic "grey zone," an area where non-heart-failure conditions may result in BNP elevations. As noted above, both age and female gender can cause mild elevations of BNP (100–200 pg/mL) that are not indicative of LV dysfunction (52, 54). Additionally, any disease process that increases right heart pressures will lead to an elevation of BNP, including pulmonary emboli, chronic obstructive lung disease (COPD), and primary pulmonary hypertension (52, 55, 56). Recently, sepsis has been shown to increase circulating BNP levels (57).

Lastly, concerns exist over the accuracy of BNP assays in the setting of renal dysfunction.

Key Concepts

1. Despite the enormous impact of heart failure on our society, our approach to the treatment of ADHF has changed little in the past 4 decades.
2. As with any disease, treatment strategies in ADHF should be based on the accepted model of disease.
   a. Emphasis on diuresis as the primary therapeutic intervention has limitations, particularly in advanced disease.
   b. The use of vasodilator therapy provides rapid improvement in cardiac performance by altering loading conditions in the failing heart.
   c. Attention to neurohormonal pathways may help slow disease progression and speed return to a compensated state.
3. Differentiating ADHF from other causes of dyspnea can be difficult, as historical elements, physical exam findings, and radiographic results lack adequate sensitivities to accurately identify the disease.
4. Natriuretic peptide levels (BNP and NT-BNP) are often helpful in identifying or ruling out ADHF; however, given frequent "grey zone" results, they must be interpreted in the context of other clinical information.

Several studies indicate that BNP levels increase in renal patients in the absence of overt heart failure (58, 59). Though the impact of renal dysfunction on circulating BNP levels has not been clearly defined, the role of nonrenal clearance mechanisms and underlying patient substrate should be considered. Since BNP is cleared primarily by intracellular endopeptidases and clearance receptors, with renal filtration playing a minor role, the elevated BNP levels noted in patients with renal dysfunction may be reflective of volume and cardiac issues commonly associated with this patient group rather than renal failure itself (52). This idea is supported by a study of end-stage renal patients that found that BNP levels were only elevated in those patients with concurrent left ventricular (LV) hypertrophy (58).

Regardless of the cause, indeterminate results are not uncommon with BNP testing. In the Multinational Study, 40% of all patients with acute dyspnea had BNP levels in the "grey zone" range, as did 50% of patients ultimately diagnosed with ADHF (51). As a result, BNP testing can be expected to provide inconclusive results approximately 40% of the time, indicating the importance of incorporating BNP levels into the larger clinical picture to confirm the presence or absence of ADHF (53). Despite these limitations, the excellent negative predictive value of a low BNP level (< 80 pg/mL) can be helpful in ruling out congestive heart failure (CHF) as a cause of a patient's dyspnea (53).

Although not studied as extensively as BNP, N-terminal BNP (NT-BNP) does appear to be useful as a diagnostic tool for ADHF. In an early study of 95 patients with suspected LV dysfunction, Fischer et al. found that BNP and NT-BNP had similar sensitivities (93% and 90%, respectively) and specificities (79% and 66%, respectively) for identification of impaired ventricular function (60). Of more relevance to the emergency physician, Lainchbury et al. compared BNP to NT-BNP in 205 patients presenting with acute dyspnea (61). They found BNP to be somewhat more sensitive (94% vs. 80%), while NT-BNP was more specific (87% vs. 70%) for the identification of ADHF. In this study, the assays values for both tests were highly correlated ($r=0.902$, $p<0.0001$).

From a laboratory perspective, NT-BNP assays may offer several advantages. As noted in a multicenter comparison study of 327 patient blood samples, NT-BNP remains stable in EDTA or heparinized plasma samples for 3 days at room temperature, while plasma BNP levels decline significantly after 4 hours at room temperature (62). Although irrelevant if BNP is run as a point of care assay, this liability may impact centralized laboratory testing. Additionally, NT-BNP has less than 0.01% crossreactivity with the active BNP peptide and so potentially can be used to guide treatment during nesiritide infusions (63).

Although less studied, plasma levels of NT-BNP are likely to be subject to the confounding variables listed above (pulmonary embolism, COPD, etc.) and may be more influenced by renal dysfunction than BNP. Although not clearly delineated, NT-BNP does not appear to be cleared by endopeptidases or clearance receptors, leading to speculation of a renal clearance mechanism (52). If true, this would decrease the utility of NT-BNP testing of patients with renal insufficiency.

Ultimately, given their similar diagnostic performance, it would appear that both BNP and NT-BNP are helpful in the identification of ADHF and that the choice of one assay over another should be based on institutional needs.

The other two natriuretic peptides, atrial natriuretic peptide (ANP) and CNP, have also been well studied for their possible utility in the diagnosis of ADHF. ANP, first identified and sequenced in the 1980s, has been shown to be a sensitive indicator of ventricular dysfunction. A majority of studies that have examined ANP and its precursor NT-ANP (N-terminal ANP) as a diagnostic tool have compared their levels against a measured degree of left ventricular dysfunction, often in the postmyocardial infarction setting (64–66). In these studies, sensitivities for an ejection fraction less than 40% ranged from 64–89%, with NT-ANP generally providing superior results. While it appears that both ANP and NT-ANP effectively identify LV dysfunction, two issues limit the applicability of these studies to the ED setting. First, although identification of ventricular dysfunction is certainly helpful in identifying patients at risk for ADHF, the diagnostic value of ANP levels in patients presenting with undifferentiated dyspnea has not been evaluated. Second, many patients presenting with ADHF suffer from isolated diastolic dysfunction, and the role of ANP testing is this group has not been evaluated.

CNP, derived predominantly from the vascular endothelium, has shown disappointing results as a marker for ADHF. Because plasma CNP levels are not consistently elevated in heart failure but are elevated in unrelated disease processes, it has been largely abandoned as a diagnostic tool for ventricular dysfunction (67–69).

Summary

ADHF is a disease process notable for both its increasing incidence and the severity of its prognosis. Although identification of the ADHF patient can be clinically challenging, the use of specific tools, particularly BNP testing, can improve diagnostic accuracy. Treatment strategies for ADHF should be grounded in an up-to-date understanding of the pathophysiology of the disease, as reflected by currently accepted conceptual models. Specific approaches to treatment will be more thoroughly explored in Part II of this article.

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Acute Decompensated Heart Failure:

Formulating an Evidence-Based Approach to Diagnosis and Treatment (Part II)

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Abstract

Acute decompensated heart failure (ADHF) is a disease of enormous scope and impact. Despite significant advances in our understanding of the pathophysiology of the disease, the initial treatment of ADHF has changed little in the past 40 years. This article, the second in a two-part series, will examine the emergency department approach to ADHF, including the issues of risk stratification and goal-directed therapy. It will also review therapeutic interventions, including available medications and the role of non-invasive ventilation devices for the stabilization and treatment of ADHF.

Key Words: Heart failure, natriuretic peptides, vasodilator therapy, neurohormones.

Introduction

As noted in Part I, heart failure (HF) is a disease of enormous scope and impact. Since most patients with acute decompensated heart failure (ADHF) present to the emergency department (ED), emergency physicians are in a unique position to improve both short- and long-term outcomes. This article will focus on the initial evaluation and treatment of the ADHF patient, including issues of risk stratification and goal-directed therapy, and a review of the medications available to treat the disease.

Initial Evaluation and Risk Stratification

Although heart failure represents a complex interplay between cardiac deficits and compensatory responses, the common issue across the spectrum of the disease is a primary deficit in cardiac performance. The clinical presentation of this deficit varies widely, from the patient who is asymptomatic except during periods of exertion to the patient who presents in overt shock when cardiac output is no longer able to meet end-organ metabolic requirements. Since the therapeutic requirements of these patients are significantly different, the initial assessment of the ADHF patient should be directed at determining the degree of cardiac dysfunction.

In 1976, Forrester et al. demonstrated that by using clinical findings, hemodynamic profiles reflective of cardiac function could accurately be identified in the post-myocardial infarction setting (1). Recently, this classification was evaluated for HF patients referred for evaluation in a tertiary care center (2). The results demonstrate that, based on clinical evidence of elevated filling pressures (evaluated by the presence of jugular venous distention, pulmonary crackles, or peripheral edema), and the grade of peripheral perfusion (evaluated by mental status, blood pressure, skin temperature, peripheral cyanosis, and capillary refill time), HF patients can be rapidly classified into one of four groups according to whether congestion is present (wet or dry) and perfusion is adequate (warm or cold). This classification scheme is not only helpful in directing initial therapy but has also recently been shown to correlate with six-month mortality with patients in the wet-cold profile (i.e., cardiogenic shock), not surprisingly demonstrating an increased risk of death (2).

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Glossary

ACE = angiotensin-converting enzyme
ADHERE = Acute Decompensated Heart Failure National Registry
ADHF = acute decompensated heart failure
BiPAP = bilevel positive airway pressure
BNP = B-type natriuretic peptide
BP = blood pressure
BUN = blood urea nitrogen
CCU = coronary care unit
CPAP = continuous positive airway pressure
DVT = deep vein thrombosis
ED = emergency department
ED-1 = endothelin-1
ETI = endotracheal intubation
GMP = guanosine monophosphate
HF = heart failure
K-ATPase = potassium adenosine triphosphatase
LMWH = low-molecular-weight heparin
LOS = length of stay
NIPPV = non-invasive positive pressure ventilation
NTG = nitroglycerin
PCWP = pulmonary capillary wedge pressure
PSV = pressure support ventilation
RAAS = renin-angiotensin-aldosterone system
RCT = random clinical trial
SVR = systemic vascular resistance
VMAC = Vasodilation in the Management of Acute Congestive Heart Failure
VTE = venous thromboembolism

Effective use of risk stratification tools to direct therapeutic and disposition decisions for ED patients is becoming increasingly important (3, 4). Though studies have attempted to quantify the risk of mortality and adverse events for patients hospitalized for decompensated heart failure (5–7), they are generally limited by their retrospective nature, small number of subjects, and inability to identify or evaluate low risk groups for whom ED discharge might be appropriate.

Recently, an analysis of data obtained from 65,275 patients in the Acute Decompensated Heart Failure National Registry (ADHERE) has allowed for development of a simple risk stratification scheme based on data that are easily obtained in the ED setting (8). Using recursive partitioning techniques, the authors developed a model to predict in-hospital mortality using the first 33,046 patients enrolled in the registry. This model was then tested prospectively, using data from 32,229 subsequent hospitalizations. The results demonstrate that using initial systolic blood pressure and serum levels of blood urea nitrogen (BUN) and creatinine, patients can be divided into low, intermediate, and high risk groups based on in-hospital mortality (Table 1). This tool, by enabling clinicians to classify patients based on short-term mortality risk, may be helpful in determining aggressiveness of care. The applicability of the tool to patients who could be treated and discharged from the ED is limited, however, by the inclusion of only hospitalized patients in the study.

Several trials have recently evaluated the utility of B-type natriuretic peptide (BNP) levels in predicting adverse events in patients presenting with dyspnea (9–11). One trial, which analyzed data from 464 patients diagnosed with ADHF, showed that patients with BNP < 200 pg/mL have significantly fewer adverse events at 90 days compared to patients with BNP levels above this level (9). Although 11% of patients admitted with ADHF in this study had BNP < 200 pg/mL, this degree of elevation is generally considered indeterminate for diagnostic purposes. Similarly, in a prospective trial that evaluated the predictive value of BNP levels in 325 patients presenting to the ED with undifferentiated dyspnea, patients with levels < 230 pg/mL had a 6-month end point (HF-related death, hospital admission, or repeat ED visit) of only 2.5%. On the other hand, BNP levels > 480 pg/mL in this study correlated with a 51% 6-month event rate (10).

TABLE 1
Risk Stratification for In-Hospital Mortality of Acute Decompensated Heart Failure

Clinical Feature	Mortality
Both BUN < 43 mg/dL and systolic BP > 115 mm Hg	2% (low risk)
Either BUN > 43 mg/dL or systolic BP < 115 mm Hg	5–6% (intermediate risk)
Both BUN > 43 mg/dL and systolic BP < 115 mm Hg	12–22% (high risk)

BUN = blood urea nitrogen; BP = blood pressure.

Goal-Directed Therapy

The concept of early goal-directed therapy is familiar to ED physicians. In cases of sepsis, the practice of goal-directed therapy involves targeting specific hemodynamic parameters to optimize patient outcomes. In a more general sense, the goal of aggressive reperfusion in acute myocardial infarction reflects a similar concept, with dissolution of the arterial thrombus identified as the initial therapeutic target. Traditionally, the approach to ADHF has focused primarily on reduction of symptoms as the initial goal of therapy. Given the role of vascular tone on cardiac performance and the issues of neurohormonal activation discussed in Part I, the critical question is whether an approach based purely on reduction of symptoms is too simplistic to provide optimal short- and long-term outcomes.

To answer this question it is helpful to clearly define what parameters might represent legitimate therapeutic targets in ADHF. In basic terms, HF patients typically share three physiologic abnormalities: a decline in cardiac performance, an increase in vascular tone, and varying degrees of volume retention. As pharmacologic interventions can be directed at any of these parameters, a discussion of the merits of targeting each is provided below.

Targeting Cardiac Performance with Inotropic Agents

Historically, the argument for using inotropic agents in ADHF has been based on the assumption that HF is a result of progressive volume overload in the setting of impaired contractility (systolic dysfunction). Recently, it has been noted that for up to 50% of patients admitted for decompensated heart failure, no contractility issue exists (12). In this group, decompensation develops as a result of impaired ventricular filling, commonly referred to as "diastolic dysfunction." Although differentiating systolic from diastolic dysfunction is an important issue for prognosis and management of chronic disease, in the ED setting the end result of both processes is typically the same, i.e., elevated filling pressures which are transmitted backward to the pulmonary vasculature, resulting in transudation of fluid into the alveoli. Clearly, in patients presenting with ADHF as a result of diastolic dysfunction, targeting improved contractility as a goal of initial therapy is unlikely to improve outcomes. In fact, even among patients with known systolic dysfunction, the use of inotropic agents is somewhat controversial, since they have been shown to increase both adverse events and mortality, presumably as a result of their arrhythmogenic effects (13). Because of this, the ED use of inotropic agents in ADHF should generally be limited to the patient who presents in cardiogenic shock.

Targeting Volume Reduction with Diuretics

As reflected by registry data, volume reduction via diuresis is the most commonly accepted goal of initial therapy for the ADHF patient (14). However, this approach makes sense only if volume overload is accepted as the primary issue in ADHF. In reality, with the exception of dialysis-dependent patients, volume overload in HF is a result of falling cardiac output, not the primary cause. Although removal of fluid via diuresis will eventually improve cardiac performance, it is an inefficient mechanism to do so, particularly in advanced HF, where issues of renal insufficiency and diuretic resistance may complicate the picture (15). Furthermore, the indirect effects of loop diuretics may be counterproductive to attempts to return the patient to a compensated state, for the following reasons.

Loop diuretics have long been known to cause an increase in serum norepinephrine, renin and vasopressin levels, an effect that can result in reflex vasoconstriction and a subsequent decrease in cardiac output (16, 17). Given the prominent role of neurohormonal activation in the expression and progression of heart failure as a disease, this effect is troubling.

From a hemodynamic standpoint, it is common teaching that the administration of loop diuretics produces a vasodilatory effect that precedes any diuresis. In truth, the vasoactive effects of loop diuretics are prostaglandin mediated and have been shown to be blunted in patients receiving aspirin (18). Since many patients with heart failure have concomitant ischemic heart disease and will therefore be on chronic aspirin therapy, a vasodilatory response in this group is unlikely to occur.

Furthermore, attempts at diuresis may be initially ineffective, particularly in advanced HF. As cardiac output falls and neurohormonal activity increases, renal blood flow declines, leading to decreases in the glomerular filtration rate, limiting both diuretic delivery and efficacy (19). Additionally, chronic diuretic use leads to hypertrophy of the distal nephron with a subsequent increase in sodium resorption that manifests clinically as diuretic resistance (20). As a result, patients with advanced disease often require escalating doses of loop diuretic to obtain an adequate clinical response (15).

Finally, there is growing evidence that the high doses of diuretics often required in advanced HF may lead to worsening of renal function in the setting of ADHF (21, 22). In one case control study of 382 patients hospitalized for decompensated heart failure, high-dose diuretics were independently associated with the development of worsening renal function (21). Overall diuresis was not significantly different between either study group suggesting that the effect was not related to the development of pre-renal azotemia as a result of overdiuresis. Worsening renal function is clinically significant in the treatment of ADHF, since it has been linked to both prolonged hospital length of stay (LOS) and increased mortality after discharge (22).

Filling Pressure Reduction as the Goal of Therapy

The vast majority of patients presenting with ADHF do so with symptoms of dyspnea, the result of elevated filling pressures transmitted from the left ventricle to the pulmonary vasculature. As described in Part I, filling pressures are a function of cardiac loading conditions, suggesting that the most efficient mechanism for lowering filling pressures acutely is to target cardiac loading conditions via the use of vasodilator agents.

Elevated filling pressures have long been known to correlate with mortality in heart failure patients. In a 1994 study of 465 patients hospitalized for ADHF, the lowering of filling pressures to near-normal levels increased the 1-year survival from 64% to 81% (23). In a more recent prospective trial of 59 patients admitted for ADHF, similar results were noted (24). In this group of patients with advanced HF, aggressive filling pressure reduction was attempted with a combination of IV vasodilator therapy and diuresis. In the 68% of patients who demonstrated significant reduction in filling pressures, the cardiac death rate was reduced from 47% to 27% and rehospitalization for cardiac causes decreased from 58% to 8% during the 19-month follow-up period. Of note, a lack of adequate response in this study was linked to renal dysfunction, underscoring the importance of maintaining adequate renal function in HF patients.

Similarly, targeting filling pressure reduction with vasodilator therapy in the ED has been shown to improve short-term outcomes (25). In a 1998 study, Cotter et al. randomized 110 patients presenting with acute pulmonary edema to an initial treatment approach that emphasized either vasodilator therapy (with high-dose IV nitrates and low-dose diuretics) or aggressive diuresis (with high-dose diuretics and low-dose IV nitrates). Significantly fewer patients in the high-dose IV nitrate arm required endotracheal intubation (13%) when compared to those in the high-dose diuretic group (43%).

The Proaction Trial, a double-blinded, ED observation-unit-based study, compared standard therapy to standard therapy plus the IV vasodilator nesiritide for patients presenting with ADHF (26). In this study of 237 patients, those who received nesiritide were significantly less likely to require hospital admission after ED observation-unit treatment. Furthermore, there was a trend toward reduction of 30-day readmission rate among the nesiritide group when compared to standard therapy. This reduction was more pronounced for New York Heart Association (NYHA) class III and IV patients (29%), and for those who failed observation unit therapy and had to be hospitalized (57%), suggesting that sicker patients received more benefit from the addition of an IV vasodilator.

Finally, data from the ADHERE registry suggest that early initiation of IV vasodilator therapy results in decreased hospital length of stay (27). In this retrospective study of over 3,600 patients, those who received IV vasodilators in the ED showed a reduction in LOS of nearly 30%, from 9.5 to 6.4 days, compared to patients who received IV vasodilators after hospitalization. Although subject to the inherent limitations of retrospective data, these results support the idea that targeting filling pressure reduction as the goal of initial therapy with vasodilator therapy may result in more rapid return to a compensated state.

Treatment of ADHF

Airway Issues / The Role of Noninvasive Ventilation

As with every high acuity patient who presents to the ED, initial treatment in ADHF is directed at ensuring the adequacy of the patient's airway, breathing, and circulation. Many patients with ADHF present in respiratory distress, and common indications for endotracheal intubation (ETI) apply, with the caveat that the respiratory symptoms that accompany decompensated heart failure reflect cardiovascular rather than pulmonary pathology and are therefore often rapidly reversible. This point is important because, in many cases, aggressive lowering of filling pressures with vasodilator agents may avert the need for ETI (25).

Patients with moderate-to-severe ADHF incapable of maintaining a peripheral oxygen saturation greater than 90% despite the use of a non-rebreather mask, may be appropriate for mechanical support by non-invasive positive pressure ventilation (NIPPV). NIPPV consists of continuous positive airway pressure (CPAP), bilevel positive pressure ventilation (BiPAP) or pressure support ventilation (PSV). CPAP is typically provided by a device that generates high flow oxygen with a unidirectional preset valve capable of maintaining a constant positive pressure throughout the respiratory cycle. The associated positive intrathoracic pressure recruits collapsed alveoli, counteracts capillary transudation of fluid and reduces the ventricular filling pressure by acting directly on ventricular and atrial walls (28).

BiPAP and PSV require a device capable of switching between different levels of pressure during the respiratory cycle. In the former technique, the ventilator cycles are based on preset times and there is no synchronization with patient breath. In PSV, the ventilator is capable of sensing a patient's inspiratory effort (which causes a rapid decline of pressure and negative flow in the circuit) and delivers the higher level of pressure to coincide with inspiration. By optimizing patient-ventilator synchronization, this system reduces the work of breathing. Regardless of the technique employed, the aim of NIPPV is to ventilate and oxygenate patients without ETI, until symptomatic improvement occurs as a result of pharmacologic therapy (29).

Multiple studies suggest that NIPPV is effective at improving gas exchange and reducing the need for ETI in ADHF patients (28, 30–33). CPAP has been shown to be safe and effective for selected patients and is often considered the technique of choice when NIPPV is considered (28, 30). Data regarding BiPAP remains somewhat controversial, as an early, randomized trial comparing CPAP to BiPAP demonstrated higher rates of myocardial infarction in the BiPAP group (31). This finding, perhaps related to the inclusion of more patients with complaints of chest pain in the BiPAP group, may reflect inadequate randomization rather than risks inherent in the technique itself (33).

In a recent ED-based prospective trial that randomized 80 patients presenting with cardiogenic pulmonary edema to CPAP, BiPAP, or oxygen via face mask in addition to standard therapy, no cardiac ischemic complications were noted with either NIPPV group (33). Endotracheal intubation rates were dramatically reduced with both types of NIPPV (7%) when compared to the oxygen-by-face-mask group (42%), suggesting that either CPAP or BiPAP provides a safe, effective means to avoid ETI during the time interval required for medication-related improvement. For successful application of NIPPV, close monitoring, hemodynamic stability and patient cooperation are required. Indications and contraindications for NIPPV are presented in Table 2.

Circulatory Issues / Cardiogenic Shock

Once immediate airway issues are addressed, a rapid assessment of circulatory function should be performed, since this will guide initial pharmacologic therapy. As described above, the hemodynamic profile of the ADHF patient can be determined at the bedside, based on the presence or absence of congestion (reflective of filling pressures) and the adequacy of perfusion (indicative of pump function) (1). For patients presenting with clinical evidence of cardiogenic shock, initial therapy should be directed toward improving end-organ perfusion via inotropic and vasopressor agents.

Inotropic agents are drugs that improve cardiac contractility by increasing the amount of intracellular calcium available to the myocardium (34). As perfusion pressure is a direct reflection of cardiac output and systemic vascular resistance, augmenting contractility provides a potentially effective mechanism for blood pressure support in this setting. Because the benefit of inotropic agents is predicated on improving systolic function, indications for ED use should include patients with known or suspected systolic dysfunction, clinical evidence of shock, and signs of pulmonary congestion (wet-cold profile). In the absence of congestion (dry-cold profile), an initial small fluid challenge (normal saline: 100–250 mL bolus) may be appropriate, since low cardiac output in this setting may be a reflection of hypovolemia secondary to overdiuresis or other volume loss rather than contractility related.

There is little evidence to guide clinicians regarding choice of individual inotropic agents. Available studies are not easily applied to many acute patients, since they involved patients in the post-myocardial-infarction setting, a situation where inadequate cardiac output may not be a direct result of systolic dysfunction (i.e. papillary muscle or ventricular wall rupture) (35, 36). Agents are typically classified according to their primary mechanism of action, with individual drugs showing significantly variable inotropic and peripheral vascular effects.

TABLE 2

Contraindications to Noninvasive Positive Pressure Ventilation

1. Respiratory or cardiac arrest
2. Altered mental status / inability to cooperate
3. Hemodynamic instability
4. Upper airway obstruction
5. Facial deformity that precludes adequate seal

Catecholamines. The actions of catecholamines depend on their affinity for specific adrenergic receptors, a phenomenon that is both medication and dose related. In general, catecholamines provide inotropic effect via activation of cardiac beta-adrenergic receptors and vasoconstriction via activation of peripheral vascular alpha-receptors.

Dopamine is a catecholamine that acts primarily on beta-receptors at low doses (2–5 micrograms/Kg/min) and on beta- and alpha-receptors at higher doses (> 10 micrograms/Kg/min). It has a dose-dependent positive inotropic, chronotropic, dromotropic and vasoconstrictor effect. The vasoconstrictor effect results in an increase in systemic vascular resistance that limits its utility in the setting of severe systolic dysfunction, where increases in afterload result in decreased cardiac output. Furthermore, the chronotropic effects of dopamine result in tachycardia and consequently an increase in myocardial oxygen demand, potentially worsening ventricular performance in this setting. Because of these issues, dopamine is generally used in combination with other, more potent inotropic agents for the treatment of cardiogenic shock (34).

Dobutamine is a synthetic catecholamine with relatively selective action on cardiac beta1 receptors. It also has a moderate beta2 and a mild alfa2 affinity at high doses. The result is an agent with primarily inotropic and mild vasodilatory effects. Although this combination makes it attractive for the management of refractory systolic heart failure, its vasodilatory properties make it unsuitable as a lone agent for the patient in frank shock. For patients presenting with mild hypotension (systolic blood pressure between 80 and 90 mm Hg), dobutamine can be initiated as a single agent; and if symptomatic hypotension persists, dopamine can then be added. Dobutamine is typically started at 2–7 micrograms/kg/min and titrated up to 20 micrograms/Kg/min based on the hemodynamic response.

Phosphodiesterase inhibitors. Amrinone and milrinone enhance the entry of calcium into myocardiocytes via phosphodiesterase inhibition. Though potent inotropic agents, their prominent vasodilatory effects limit their utility in the hypotensive patient. Although interest has developed regarding the utility of adding milrinone to standard therapy for the treatment of refractory systolic HF, a recent trial found that milrinone provided no benefit compared to placebo and was associated with higher incidence of symptomatic hypotension and new atrial arrhythmias (37).

Calcium sensitizers. Levosimendan belongs to a promising new class of inotropic agents called "calcium sensitizers," which act by increasing sensitivity of troponin-C to intracellular ionized calcium, as well as causing peripheral vasodilation by opening potassium adenosine triphosphate (K-ATPase) channels in vascular smooth muscle cells. One randomized prospective study of 203 low-output HF patients suggests that levosimendan is more effective than dobutamine at improving hemodynamic parameters, as measured by cardiac output and pulmonary "capillary" wedge pressure (PCWP) (38). In this study, lower mortality through 180 days was also noted in the levosimendan group. Although these results are intriguing, further study is required and currently levosimendan remains an investigational drug.

Pharmacologic Options for the Hemodynamically Stable Patient

For most patients presenting with ADHF, adequate perfusion exists. In this group, as discussed above, a growing body of evidence suggests that the goal of therapy should be an early and sustained reduction in filling pressures. Vasodilator therapy, by favorably altering cardiac loading conditions, offers the most efficient mechanism to achieve this goal. There are several classes of vasodilators currently available for the treatment of ADHF. The choice of agent and route of delivery (oral vs. IV) should be based on the severity of the presentation and the likely disposition of the patient.

Vasodilator Drugs

Nitrates. Nitroglycerin (NTG) is the vasodilator most commonly used for the treatment of ADHF. It acts by increasing intracellular levels of cyclic guanosine monophosphate (GMP), resulting in venous and, for higher doses, arterial vasodilation. The advantages of NTG include low cost, patient comfort and a proven safety profile. Additionally, in patients requiring a rapid therapeutic effect or in those in whom IV access is being obtained, sublingual NTG has been shown to provide a rapid hemodynamic response (39, 40).

Interestingly, the hemodynamic efficacy of sublingual nitrate preparations may not be noted with intravenous preparations administered at usual doses. Data from a study of ADHF in which one group of patients underwent invasive hemodynamic monitoring found that significant reduction of PCWP did not occur until the intravenous NTG dose was well above 100 micrograms per minute (41). This was more than twice the mean dose received by patients treated without invasive monitoring, suggesting that physicians were unlikely to achieve adequate dosage unless a PCWP was available to guide therapy.

Suboptimal dosing aside, there are two primary obstacles to the effective use of NTG, the phenomenon of tolerance and its effect on neurohormonal pathways. "Tolerance" refers to the progressive attenuation of pharmacologic effect that develops rapidly in high-dose nitrate therapy, limiting efficacy without continuous monitoring and upward dose titration (42). In the study referenced in the previous paragraph, investigators found that maximal wedge pressure reduction with NTG occurred within the first 3 hours of therapy but gradually normalized over the following 21 hours despite intervening diuresis and upward nitrate dose titration, presumably a reflection of the effect of tolerance (41).

Though the phenomenon of tolerance is complex and poorly understood, there is evidence that nitrate-induced neurohormonal activation may play a significant role (43). Several studies have demonstrated an increase in plasma concentrations of catecholamines, renin and endothelin with continuous nitrate therapy (44–46). As the vasoconstrictive effects of neurohormonal pathways progressively overshadow the vasodilatory effect of nitrate therapy, the clinical manifestation of tolerance may become apparent. Given the importance of neurohormonal activation in the development and progression of heart failure, this potential etiologic mechanism for the phenomenon of tolerance raises questions about the suitability of continuous nitrate therapy in ADHF patients.

As with any vasodilator, nitrates must be avoided in the presence of hypertrophic cardiomyopathies or severe aortic stenosis, since they will increase the obstructive gradient and reduce cardiac output. Furthermore, vasodilators must be used with caution in patients with hypoperfusion or evidence of right ventricular myocardial infarction, since both of these conditions are pre-load dependent. When patients become acutely hypotensive during nitrate infusions, these conditions must be ruled out and the etiology of ADHF re-considered.

Sodium nitroprusside. Nitroprusside is perhaps the most potent arterial vasodilator available. Although its short half-life and rapid effect make it an appealing agent for the treatment of ADHF, its monitoring requirements limit its applicability to most ED patients. Furthermore, nitroprusside is metabolized to thiocyanate—a potential source of toxicity for infusions lasting more than 24 hours.

ACE Inhibitors. Angiotensin-converting enzyme (ACE) inhibitors have been shown in multiple studies to decrease mortality in chronic HF. Although there is less data regarding their use in ADHF, ACE inhibitors have been shown to be effective vasodilators in this setting (40, 47, 48). In one study of 24 ADHF patients randomized to receive either nitroglycerin or captopril sublingually, captopril was shown to be as effective at decreasing preload and afterload as nitroglycerin. One noted benefit of captopril was its longer duration of action, with return to baseline hemodynamics not occurring for 2–3 hours after administration of the medication. Though this duration of action is an improvement over sublingual NTG, the 8-hour recommended dosing interval means that captopril is unlikely to provide the sustained reduction in filling pressures desired in ADHF.

Regarding their effect on neurohormonal activation, ACE inhibitors clearly inhibit activation of the renin-angiotensin-aldosterone system (RAAS) system, but their effect on adrenergic tone and endothelin activity is less clear (47). Interestingly, ACE inhibitors have been shown to decrease the diuretic and natriuretic effect of loop diuretics. In two prospective studies with a total of 37 HF patients, the diuretic effect of furosemide was compared after pretreatment with captopril or placebo (49, 50). In the groups that received captopril, diuresis decreased 41–43%. Given the small size of these studies, the clinical relevance of this issue is not clear. Because ACE inhibitors have been clearly shown to decrease mortality in chronic heart failure, they should be started in every patient within the first 24 hours of admission and in any case before hospital discharge if no contraindications are present (51).

Nesiritide. Nesiritide is a synthetic form of b-type natriuretic peptide (BNP) that was approved by the Food and Drug Administration (FDA) for use in ADHF in 2001. As an analog of the body's own counter-regulatory hormone, it embodies many of the characteristics desired of an ideal agent for the treatment of ADHF. The beneficial hemodynamic effects of BNP in ADHF have been demonstrated in multiple studies, with early work focusing on the vasodilatory effect of escalating doses of BNP given either as a bolus or an infusion.

In one early study, nesiritide was found to provide a dose-related decrease in PCWP, systemic vascular resistance (SVR), mean pulmonary artery pressure and mean arterial pressure when given as a bolus to HF patients (52). At the highest doses, PCWP and SVR were reduced by 73% and 53%, respectively. A similar effect was noted in a subsequent study in which patients were given a 90-minute infusion of BNP (53). In this trial of 20 patients with "severe" HF, the infusion resulted in a mean decrease of PCWP from 25.1 mm Hg to 13.2 mm Hg.

In a 1999 multicenter random clinical trial (RCT) with 103 heart HF, a 24-hour infusion of nesiritide was found to produce significant reductions in PCWP (27–39%) that were dose dependent (54). Additionally, increases in cardiac index and stroke volume index were noted, with no concomitant change in heart rate, suggesting that the improvement in cardiac performance did not come at the expense of increased myocardial oxygen demand. The beneficial hemodynamic effects of BNP in this study were noted within 1 hour of initiating the infusion and were maintained through the duration of treatment. These results were replicated in a subsequent RCT of 127 HF patients (55). In this study, nesiritide use resulted in a 6-hour reduction of PCWP of 6 and 9 mm Hg (dependent on dose) and improvements in global clinical status in 60–67% of patients.

In the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial, 489 patients with ADHF were randomized to receive either nesiritide, IV NTG, or placebo (56). The placebo group was subsequently randomized into one of the active treatment arms after 3 hours. The primary end points included change in PCWP (catheterized group only) and change in dyspnea symptoms at 3 hours. Significant change in the PCWP at 3 hours was noted in the nesiritide group but not the NTG group when compared with placebo. A recently published subgroup analysis of patients from the VMAC trial who all underwent invasive hemodynamic monitoring demonstrated that patients treated with nesiritide had a mean reduction of PCWP of 6.5 mm Hg at 1 hour and 12.2 mm Hg at 24 hours. The available evidence suggests that nesiritide is a potent vasodilator that provides both early and sustained reduction in filling pressures in the ADHF patient.

The potential benefits of nesiritide extend beyond its efficacy as a vasodilator. Natriuretic peptides have long been known to attenuate neurohormonal activity, and not surprisingly, nesiritide has been shown to decrease sympathetic tone as well as inhibit production of renin, aldosterone and endothelin (57–59). These effects presumably not only help speed return to a compensated state in the acute setting but may also slow disease progression, a process that appears to be largely mediated via neurohormonal pathways.

Additionally, BNP promotes natriuresis and diuresis at the level of the kidney while maintaining glomerular filtration rate and renal blood flow (57, 60). Although clinically this effect appears to be limited, nesiritide use has been noted to lessen diuretic requirements in coronary care unit (CCU) patients and in patients with renal insufficiency when compared to NTG (61, 62).

A recent article has raised concerns about the effect of nesiritide on renal function in decompensated heart failure (63). This meta-analysis of 5 randomized controlled trials found that compared to controls, patients treated with nesiritide had an increased risk of developing worsening renal function, defined as an increase in serum creatinine of > 0.5 mg/dL (relative risk 1.54; 95% CI 1.20–1.99; p=0.001). However, the results of this study are limited by the authors' lack of access to primary data and the inclusion of many patients who received drug infusion rates well above the approved dosing range. The latter point is important, since symptomatic hypotension, and thus the potential for renal hypoperfusion, becomes much more common as the dose of nesiritide increases. Regardless of the etiology, these results contradict the commonly held belief that nesiritide provides a degree of renal protection during treatment of ADHF. This belief is based on several potentially beneficial renal actions, including effects on efferent and afferent vascular tone and inhibition of renin synthesis. In the near future, the effect of nesiritide on renal function in ADHF will be more definitively addressed by a multicenter prospective trial of approximately 1,900 patients, currently underway in Europe (64).

A more frequently voiced concern about widespread use of nesiritide is its cost. Interestingly, there is evidence that the use of nesiritide may decrease the overall cost of care. This is likely a reflection of the fact that the bulk of costs associated with treatment of any disease are not a function of the price of medications as much as hospital LOS. For heart failure patients, medications have been shown to represent approximately 10% of the total cost of care (65). Of more importance in overall cost of care for HF is patient recidivism and frequent hospital readmission. The six-month readmission rate for patients with ADHF is approximately 25%, but it increases to over 45% in high-risk groups (66). Successful treatment of ADHF from a financial perspective, therefore, should presumably focus on decreasing hospital LOS and readmission rates.

In one study, nesiritide was shown to decrease health care resource utilization and LOS for patients admitted to the CCU (63). In this retrospective, case-controlled evaluation of 216 heart failure patients admitted to the CCU, patients who received nesiritide showed a significant decrease in CCU LOS and decrease in health care resource costs, even when the price of the drug was included. The PROACTION study demonstrated a reduction in costs for patients treated with nesiritide compared to standard therapy in an ED observation unit (26). Cost reduction was apparently secondary to a decrease in admission rate, readmission rate, and shorter LOS on readmission. Although further study in the form of large prospective trials is needed, the available evidence suggests that the added expense of using nesiritide for the treatment of ADHF may be offset by the benefits, specifically by decreases in hospital LOS and readmission rates.

Many of the potential benefits offered by nesiritide for the treatment of ADHF are a result of both its efficacy as a vasodilator and its ability to provide neurohormonal blockade, actions that are intimately related. The impact of these effects on important outcomes (hospital LOS, readmission rates, and mortality) has yet to be delineated by large, randomized, controlled trials.

Diuretics. Clearly, effective management of ADHF cannot be accomplished without the use of diuretics. Yet given their known neurohormonal effects and their potential link to worsening renal function at high doses, the frequent use of loop diuretics as the primary therapeutic agent for ADHF needs to be questioned. Increasingly, it would appear that ideal therapy during episodes of decompensation should include diuretics as one part of an approach that places primary emphasis on the early and sustained control of filling pressures with vasodilator therapy. For patients who present with mild decompensation, particularly in the setting of known dietary indiscretion or medication noncompliance, an initial trial of diuresis without the addition of an IV vasodilator may allow for resolution of symptoms and avoidance of hospital admission.

When treating ADHF, loop diuretics should be administered intravenously, as bowel wall edema can delay absorption (34). Furosemide, the most commonly used diuretic, should initially be administered at a dose equal to twice the patient's usual dose. If ineffective, repeat dosing at double the initial amount can be attempted. All loop diuretics cause potassium and magnesium depletion and at high doses can lead to ototoxicity. Data from the SOLVD trial, in fact, suggest a higher mortality for chronic heart failure patients treated with loop diuretics, probably a result of hypokalemic-related arrhythmias (67). Adequacy of response to therapy should be based on improvement of symptoms and urinary output, which generally should exceed 500 mL after two hours.

Diuretic resistance, which often accompanies advanced HF, necessitates escalating diuretic doses, a situation that has been linked to worsening renal function and prolonged hospitalization (21, 22). In this setting, the use of continuous diuretic infusions has been shown more effective than bolus therapy in achieving an adequate response (68). In one prospective case control study of elderly, class IV ADHF patients, delivering furosemide as a constant infusion resulted in a mean diuresis of 5.0 liters in the first 24 hours of therapy and 14 liters over the duration of treatment (69). This group had an average hospital LOS that was 2.3 days shorter than matched controls, resulting in a cost savings of $5,249 per patient as calculated by the authors of the study. Additionally, renal function in the infusion group remained relatively stable, with an average change in serum creatinine of 0.2 mg/dL during the treatment period. Although more study is required to determine the applicability of this approach to all ADHF patients, it would appear that continuous furosemide infusion offers an efficacious alternative to high-dose bolus therapy in patients with advanced disease.

Anticoagulant therapy. The importance of venous thromboembolism (VTE) as a frequent contributor to morbidity and mortality among patients hospitalized for medical conditions has been noted in multiple studies (70–72). Consistently, admission for ADHF is noted as an independent risk factor for the development of VTE, particularly among patients with significant left ventricular dysfunction (73). For patients hospitalized with high-risk medical conditions (ADHF, chronic obstructive pulmonary disease, systemic infections) the risk of deep vein thrombosis (DVT) has been reported at approximately 16% (72). A recent review of two RCTs that evaluated the efficacy of different low-molecular-weight heparin (LMWH) formulations compared to placebo for prevention of VTE in 4,783 medical patients found a 50% reduction in VTE with a non-significant increase in major bleeding in the LMWH groups (73). These and similar results have led expert panels to recommend consideration of thromboprophylaxis for all patients admitted for ADHF, particularly those over the age of 60 (72, 73). Prophylaxis can be provided with either LMWH (i.e., enoxaparin 40 mg or dalteparin 5000 IU) or unfractionated heparin (5000 IU) although a recent meta-analysis of 9 trials comparing LMWH to unfractionated heparin found a trend toward greater reduction of DVT in the LMWH group (74).

Newly Emerging Drugs

A number of investigational drugs are currently under development for the treatment of ADHF, several targeting neurohormonal blockade, specifically endothelin and vasopressin pathways. Endothelin-1 (ET-1) is a potent vasoconstrictor that is increased in ADHF, and tezosentan, an ET receptor blocker, has recently emerged as a promising therapeutic agent. Four studies have been done focusing on the safety and efficacy of tezosentan. One study, in which 292 ADHF patients were randomly assigned to tezosentan or placebo in addition to standard therapy, found that tezosentan decreased both symptoms and PCWP more than placebo, with a positive trend in patient outcomes in the tezosentan group (75). These results are encouraging but preliminary.

Vasopressin acts through peripheral receptors mediating both vasoconstriction (V1 receptor) and water retention in the renal tubules (V2 receptor) (76). After experimental observations indicated that vasopressin levels are elevated in ADHF, interest developed in the role of vasopressin receptor blockade as a mechanism for treatment for the disease. Tolvaptan, a V2 receptor antagonist, has been shown in preliminary studies to increase urine output in HF patients, decreasing edema and body weight during hospitalization while increasing serum sodium in hyponatremic patients. Although potentially beneficial, tolvaptin has yet to demonstrate clinical benefit over standard therapy (76).

Summary

Heart failure is a disease whose incidence and impact are expected to rise in the coming decades, mandating development and application of evidence-based treatment strategies. Although ultimately this will require large, ED-based prospective trials, the evidence currently available underscores the importance of filling pressure reduction as both the initial and long-term goal of heart failure care. To this end, the use of IV vasodilator therapy, with attention to issues of neurohormonal activation, appears to provide the most efficient mechanism for rapid resolution of symptoms and slowing of disease progression.

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New Diagnostic and Treatment Modalities for Pulmonary Embolism:

One Path through the Confusion

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Abstract

Pulmonary embolism is one of the greatest diagnostic challenges in emergency medicine. New techniques and strategies constantly arise for the diagnosis and treatment of this disease. A review of the new diagnostic and treatment modalities for pulmonary embolism (PE) suggests that it should be suspected in any patient with unexplained dyspnea, tachypnea, or chest pain. All patients suspected of PE must be risk stratified, ideally with a criteria-validated clinical decision rule. After assessing pre-test probability, D-dimer assays will reliably exclude PE in the low risk group and no further imaging is warranted. Computed tomography (CT) angiogram is the initial imaging study of choice for stable patients. V/Q scans should be used only when CT is not available or if the patient has a contraindication to CT scans or intravenous contrast. Bedside echocardiography or stabilization of the patient and CT angiogram are the initial tests for suspected massive PE. If PE is confirmed, hypotensive patients should be treated with thrombolytics. Both heparin and low molecular weight heparin are equally effective initial treatments for stable patients with suspected or confirmed PE.

Because accurate screening and identification of pulmonary embolism frequently requires more than a single test, knowledge of existing diagnostic techniques allows an evidence-based strategy for diagnosis. New therapeutic choices may benefit patients with confirmed pulmonary embolism.

Key Words: Pulmonary embolism, D-dimer, CT angiogram, chest pain.

Introduction

PULMONARY EMBOLISM (PE) is one of the most enigmatic disease processes facing emergency medicine. Its high incidence, morbidity, and mortality are compounded by the difficulty of making the diagnosis. If syphilis is the "great masquerader," then surely pulmonary embolism is the "great trickster." It can present insidiously, eludes simplistic diagnostic strategies, and if not treated, can kill our patients. The importance of this clinical entity is reflected in the approximately 1,000 articles published each year, as well as ever-changing practice guidelines, which reflect advances in the relevant technology, assays, and medications.

Recently two major organizations, the American College of Emergency Physicians (ACEP) and the British Thoracic Society (BTS), separately revised guidelines for the evaluation and management of suspected pulmonary embolism (1, 2). This article will concentrate on recent changes in the diagnosis of PE, as well as new treatment options for emergency department (ED) patients.

Epidemiology

The incidence of PE in the United States is estimated at 600,000 cases per year (3); it results in 50,000 – 200,000 deaths annually (4). Early estimates from the 1970s and 1980s suggest that roughly two-thirds of fatal PEs were undiagnosed until autopsy (3, 5). Short-term survival rates for PE were originally reported at 77 – 94% (6 – 9). One cohort study using data for 1966 – 1999 demonstrated a 59% thirty-day survival rate and 48% one-year survival rate for patients diagnosed with pulmonary embolism (10). Patients presenting with hypotension have had a higher initial mortality rate (up to 30%) (11) than do patients with co-morbidities such as congestive heart failure, malignancy, and neurological disease (10). However, Calder et al. in 2005 pointed out that much of this mortality data was overestimated, based on inpatient or autopsy populations, while analysis of untreated or missed pulmonary embolism in ambulatory patients treated in the ED had recurrence rates and mortality less than 5% (12).

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Glossary

ABG = arterial blood gas
ACEP = American College of Emergency Physicians
ACLS = advanced cardiac life support
BTS = British Thoracic Society
CT = computed tomography
CTA = CT angiogram
CTV = CT venogram
D/C = discharge
DSA = digital subtraction angiography
DVT = deep venous thrombosis
Dx = diagnosis
ED = emergency department
ELISA = enzyme-linked immunosorbent assay
JVD = jugular venous distention
LE = lower extremity
LMWH = low-molecular-weight heparin
LR = likelihood ratio
MDA = trademark for a type of D-dimer
PA = pulmonary artery (angiogram)
$PaCO_2$ = arterial partial pressure of carbon dioxide
PaO_2 = arterial partial pressure of oxygen
PE = pulmonary embolism
PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis
TEE = transesophageal echo
V/Q = ventilation/perfusion
VTE = venous thromboembolism

Pathophysiology

Pulmonary embolism is commonly a sequela of thrombosis of the deep veins of the legs or pelvis. Less commonly, the origin of the clot is the vena cava, an upper extremity, or even the hemorrhoidal vein. Approximately 70% of patients on diagnosis with PE have a proven deep venous thrombosis (DVT), and it is assumed that the other 30% have a DVT that has already been dislodged (13).

Risk factors for thrombosis, and consequent PE, include those associated with Virchow's triad: stasis, trauma, and hypercoagulability. The major risk factors are abdominal/pelvic surgery, hip/knee replacement, late pregnancy, c-section, lower limb fracture, abdomen/pelvis/advanced malignancy, immobility, as well as previous PE. Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), a study validating the use of nuclear lung scanning with a pulmonary angiogram, provides excellent data on the clinical manifestations of PE (14). Fifty-six percent of patients with PE in the PIOPED study had immobility, making this the most common factor (14). Minor risk factors (Table 1) include congenital heart disease, congestive heart failure, hypertension, superficial venous thrombosis, indwelling venous catheters, chronic obstructive pulmonary disease, oral contraceptives/estrogen replacement therapy, neurologic disability, long distance travel and obesity (2). Increasing use of indwelling central catheters in the subclavian vein have made upper extremity DVTs more common than in the past, accounting for up to 20% of pulmonary embolisms in some studies (15, 16). Cigarette smoking is believed to be a minor risk factor, although this was not confirmed in one recent study (17). When patients with PE are tested, thrombophilias such as Factor V Leiden, antiphospholipid antibody syndrome, and protein C and S deficiencies are present in 25–50% of patients with confirmed PE (18). It is important to note that multiple risk factors are often present in patients with pulmonary embolism; some of these risk factors may be synergistic. For example, Factor V Leiden increases the risks of thromboembolism by 3–5-fold, but combined with estrogen use it rises to 35-fold (2, 13, 18).

TABLE 1
Risk Factors for Pulmonary Embolism

Major Risk Factors for PE
Immobility
Abdominal/pelvic surgery
Hip/knee replacement
Late pregnancy
C-section
Lower limb fracture
Abdomen/pelvis/advanced malignancy
Previous PE
Minor Risk Factors for PE
Congenital heart disease
Congestive heart failure
Hypertension
Superficial venous thrombosis
Indwelling venous catheter
Chronic obstructive pulmonary disease
Oral contraceptives/estrogen therapy
Neurologic disability
Long-distance travel
Obesity
Smoking

Source: reference 2.

Diagnosis

The signs and symptoms of pulmonary embolism overlap with those of many other disorders, making it a challenge of when to include it in the differential diagnosis of patients presenting with a nonspecific complaint. Data from the PIOPED study demonstrate that over 97% of patients with confirmed PE had dyspnea, tachypnea, or chest pain. Therefore, at the minimum, it is prudent to consider PE in any patient with one of these manifestations without a clear alternative diagnosis.

The clinical manifestations of pulmonary embolism run the gamut of frank hypotension and respiratory instability to no signs or symptoms at all. Massive PEs may present in cardiac arrest, with syncope, or with enough right heart strain to cause elevations of troponin (19–22). However, the most common presenting symptom in any PE is dyspnea, which occurs in approximately 75% of patients, with sudden onset dyspnea having a higher predictive value (15, 23). Chest pain, usually pleuritic in nature, is the second most common symptom, reported in 66% of PIOPED patients (14). Other symptoms include cough, hemoptysis, syncope, palpitations, wheezing, and leg pain (24). Patients may also be relatively asymptomatic (25), especially younger, healthy adults (26).

Physical examination also reveals various signs in a patient with PE. Patients may have tachypnea, tachycardia, rales/wheezing, fever, S3 or 4, leg edema, or jugular venous distention (JVD) (15, 21). Tachypnea (>16 breaths/ minute) is frequently identified as the most common sign of PE, with tachycardia (>100 beats/ minute) as the next most common (Table 2). As many ED patients present with one of these two signs, their specificity for PE is limited. PE may also be associated with fever, with or without radiographic changes, and thus potentially misdiagnosed as pneumonia.

The ECG on presentation will most commonly show sinus tachycardia with non-specific ST/T wave changes (24). Incomplete right bundle branch block is also frequently seen (27). The classic S1Q3T3 is reported in only 20% of patients; though suggestive, it is certainly not pathognomonic, since it may be present in any patient with right heart strain of any etiology (28).

Risk Stratification

When PE is considered, systematic risk stratification should be performed to help decide which additional diagnostic tests to perform. Accurate identification of PE relies heavily on an estimation of the patient's risk, to specify any subsequent testing.

The most objective way to perform risk stratification is through the use of a clinical decision rule. There are three clinical decision rules, which have been validated for the ED population: the Wells Criteria (29), the Wicki Criteria (30) and the Charlotte (also known as Kline) Criteria (31).

TABLE 2
Symptoms and Physical Signs of PE

Common Symptoms in Patients with PE	**Percentage of Patients with Symptom**
Dyspnea	84%
Pleuritic chest pain	74%
Apprehension	59%
Cough	53%
Hemoptysis	30%
Sweating	27%
Non-pleuritic chest pain	14%
Common Physical Signs in Patients with PE	**Percentage of Patients with Sign**
Tachypnea > 16 breaths/min	92%
Rales	58%
Accentuated S2	53%
Tachycardia > 100 beats/min	44%
Fever > 37.8°C	43%
Diaphoresis	36%
S3 or S4 gallop	34%
Thrombophlebitis	32%
Lower extremity edema	24%
Cardiac murmur	23%
Cyanosis	19%

Source: reference 14.

Wells Criteria for Pulmonary Embolism

The Wells Criteria decision rule consists of a point scoring method (Table 3). A score of 0-2 is interpreted as low risk, correlating with a probability of PE of 3.6%. A score of 3-6 is moderate risk with 20.5% probability of PE, while a score of greater than 6 points is high risk with a 66.7% probability of PE. One of the strengths of the Wells Criteria rule is that it relies only on the history and physical, requiring no ancillary testing for risk stratification. One problem with the Wells Criteria is the "alternate diagnosis less likely than PE" component. This component adds some degree of subjectivity to an otherwise objective rule. However, the Wells Criteria have been prospectively validated. When compared with the Wicki Criteria, the Wells Criteria showed moderate-to-substantial interrater agreement (32) and were found to reliably risk stratify pretest probability for patients with suspected PE (33).

Wicki Criteria

Unlike the Wells Criteria, the Wicki Criteria rely on ancillary testing in addition to signs and symptoms. Calculation of a Wicki score requires interpretation of both a chest radiograph and an arterial blood gas (Table 4). Scores of 0–4 are low risk with a 10% probability of PE, scores of 5–8 are moderate risk with a 38% probability of PE, and scores of 9–12 are high risk, correlating with an 81% probability.

When the predictive accuracy and concordance of the Wells and Wicki Criteria were compared (by members of the group that did the initial Wicki Criteria research), the two prediction rules were found to have similar predictive accuracy for PE among ED patients. It can be argued that the Wells Criteria are quicker, easier, and more cost-effective as well as providing results similar to those of the Wicki Criteria. Although the ACEP has not formally endorsed an individual scoring system, the Wells Criteria have the lowest pretest probability in the low risk group and are the only criteria that the ACEP recommends for use with whole blood cell qualitative D-dimer.

Charlotte Criteria

The Charlotte Criteria rule was specifically developed to determine if a patient is at low enough risk of PE to allow for diagnostically definitive bedside testing (Table 5). It stratifies patients into low-risk or high-risk groups. Among low-risk patients, PE can presumptively be excluded by the use of a D-dimer assay. If two or more of these components are present, the patient is considered at high risk with a 40% probability of PE; these patients are considered at too great a risk to allow for bedside testing (31). The lower risk group was not further subdivided and had a 13.3% probability for PE. The Charlotte Criteria results have been prospectively validated in conjunction with a diagnostic algorithm; patients deemed negative for PE through the combined use of this decision rule and the algorithm had a less than 1% false negative rate (34). Recently, a modified Charlotte Criteria rule, which excluded pregnant patients, patients > 70 years of age and patients with symptoms for more than four days, yielded a 99.9% negative predictive value for pulmonary embolism in patients with low clinical suspicion of PE, when used in conjunction with an enzyme-linked immunosorbent

TABLE 3

Wells Criteria for Assessment of Pretest Probability of Pulmonary Embolism

Criteria	Points
1. Suspected DVT	3.0
2. An alternative diagnosis is less likely than PE	3.0
3. Heart rate > 100 beats/min	1.5
4. Immobilization or surgery in previous 4 weeks	1.5
5. Previous DVT/PE	1.5
6. Hemoptysis	1.0
7. Malignancy (on treatment or treated within past 6 months)	1.0

Score	Mean Probability of PE	% of Patients with This Score	Risk
< 2	3.6%	40%	low
2–6	20.5%	53%	medium
> 6	66.7%	7%	high

Source: reference 29.

TABLE 4
Wicki Criteria for the Assessment of Pretest Probability for PE

Criteria	Points
Age 60 – 79	1
Age > 79	2
Prior DVT/PE	2
Recent surgery	3
Heart rate > 100 beats/min	1
$PaCO_2 < 36$	2
$PaCO_2 = 36-39$	1
$PaO_2 < 49$	4
$PaO_2 = 49-60$	3
$PaO_2 > 60-71$	2
$PaO_2 > 71-82$	1
Chest X-ray: plate-like atelectasis	1
Chest X-ray: elevation of hemidiaphragm	1

Score	Mean Probability of PE	% of Patients with This Score	Interpretation of Risk
0 – 4	10%	49%	low
5 – 8	38%	44%	moderate
9 – 12	81%	6%	high

Source: reference 30.

TABLE 5
Charlotte Criteria for Rapid Rule-out of Pulmonary Embolism Using D-Dimer and Alveolar Dead Space

If any two are present, patient is unsafe for rule-out of pulmonary embolism

1. Age greater than 50 years or heart rate greater than systolic blood pressure
2. Recent surgery (requiring anesthesia) in past 4 weeks
3. Unilateral leg swelling (asymmetry on visual examination)
4. Hemoptysis
5. Unexplained room air pulse oximetry < 95% (nonsmoker, no asthma, no chronic obstructive pulmonary disease)

Source: reference 31.

assay D-dimer (35). The only patient with a missed diagnosis of PE in this study had a pneumothorax that was treated, and a positive D-dimer that was disregarded due to the alternate diagnosis (35).

Risk Stratification by Clinical Opinion

Clinicians may opt to perform risk stratification without the use of a decision rule. While the opinion of experienced clinicians has showed good correlation with objective criteria (36), it is difficult to know how true this may be for all emergency physicians. It may be preferable to use one of the clinical decision rules above and augment the yielded pretest probability with clinical judgment.

Risk stratification establishes a pretest probability which then drives further testing to establish a post-test probability: the post-test probability is then used to “rule in” or “rule out” the diagnosis of PE. While each clinician must determine which thresholds to use for this purpose, driving the post-test probability below 1.5 – 2% is generally considered acceptable in excluding the diagnosis of PE. A post-test probability of 80 – 90% is generally used for ”ruling-in” the diagnosis.

The most obvious risk of missing the diagnosis is disease progression, with its inherent morbidity and mortality; not as widely considered are the risks of over-diagnosing this disorder. Patients falsely branded with a PE will be exposed to the risks of anticoagulation (37), will probably be misdiagnosed again when presenting to health care providers, and may encounter difficulties with life and health insurance.

Diagnostic Testing

Choosing which test to order first is often based on clinician preference and institutional availability. Arterial blood gas (ABG) and chest X-ray are two tests that are often ordered, but have little effect on post-test probabilities.

ABG

Many authors believe that an ABG should not be part of the routine PE workup, as studies have shown it has a low sensitivity and specificity (38–40). The incidence of a completely normal ABG approaches 40% in younger and healthier patients (39). Sensitivity for the test increases when the criteria for a positive test are arterial partial pressure of carbon dioxide ($PaCO_2$)> 35, an arterial partial pressure of oxygen (PaO_2) < 80, or an A-a gradient > 20. However, since the negative likelihood ratio (LR) using this criterion is 0.9, the ABG result has little impact on the pretest probability (40). However, it is important to note again that the Wicki and Charlotte Criteria both use an ABG as a component in calculating their respective scores.

Chest Radiograph

While the chest X-ray in the investigation of PE can lead to an alternate diagnosis such as pneumothorax or pneumonia, it usually has abnormalities that are nonspecific and non-diagnostic. Classic signs such as peripheral oligemia (Westermark's sign) and pleural wedge based densities (Hampton's hump) occur in less than 20% of patients (41–43). Conversely, up to 80% of X-rays in PE can be interpreted as abnormal when signs resulting from modification of anatomic structures (descending pulmonary arteries, elevated diaphragmatic domes, heart shadow, peripheral vessels) are taken into consideration (23, 24, 41, 42). Other X-ray signs such as densities, infiltrates, and effusions are all common with PE. Atelectasis and the resulting elevation of a hemidiaphragm are the most common X-ray abnormalities (43).

D-dimer

D-dimer is a fibrin degradation product formed by the enzymatic activity of cross-linked fibrin polymers. D-dimer is thus present in venous thromboembolism, but may also be present in malignancy, pregnancy, myocardial infarction, disseminated intravascular coagulation, sickle cell disease, and during the postoperative period (44). D-dimer levels are also correlated with position and size of the PE, and are thus highly accurate markers for segmental PEs and less accurate for peripheral subsegmental PEs (45).

The function of the D-dimer assay in the work-up of PE is to lower the post-test probability of PE; therefore, a negative result is quite useful. A positive result rarely alters our clinical suspicion significantly and therefore necessitates further testing.

There are five different types of D-dimer assays available: enzyme-linked immunosorbent assay, whole blood agglutination, latex agglutination, and the newer turbidimetric and immunofiltration assays. Each assay has different diagnostic characteristics, making generalizations of the entire class difficult.

Whole blood agglutination. The SimpliRED™ test, a qualitative red cell agglutination (whole blood assay) has been reported to have an overall sensitivity of 84.8% and a specificity of 68.4% in a 1,177 patient trial that assessed its effectiveness in diagnosing PE (46). This test is rapid and can be done in minutes, even at the bedside. It has been concluded by both the ACEP and the British Thoracic Society that this whole blood assay can indicate a sufficiently reduced risk of PE to rule out the diagnosis in a patient with low pretest probability as defined by Wells criteria (1, 2).

Enzyme-linked immunosorbent assay (ELISA). ELISA tests have shown a pooled sensitivity of 97% (47), but the conventional test may take up to 4 hours to run. In one study, a rapid ELISA test had an overall sensitivity of 95% (48) and one test in particular, the VIDAS™ , has been shown to have a sensitivity of 97%, but a specificity as low as 8% (49). A negative result on this test has been specifically shown to be of value in both the low and intermediate probability groups (48).

Latex agglutination. Latex agglutination assays have shown disappointing results when used in the diagnosis of PE. They were designed for the diagnosis of hematologic disorders such as disseminated intravascular coagulation. Given this purpose, the sensitivity suffers to yield a greater specificity; the values are 70% and 76% respectively (1) and thus should not be used in the diagnosis of PE.

Immunoassays. Immunoassays, both immunofiltration and latex particle immunoassays, are new and promising. The MDA™ latex particle immunoassay has demonstrated sensitivities of 97–99% (49, 50).

Turbidimetric. The turbidimetric assays utilize another, newer form of D-dimer; these assays have shown a pooled sensitivity of > 95% (49), but take two hours to yield results.

The British Thoracic Society and the ACEP agree on a level B recommendation that D-dimer should only be considered after assessment of clinical probability, and that D-dimer cannot be used as a lone test to rule out PE in the high pretest probability cohort. The ACEP has assigned a level B recommendation for using a negative D-dimer to exclude PE in low Wells pretest probability patients with a negative whole blood assay (i.e., SimpliRED™). A level C recommendation was given for the use of the whole blood (SimpliRED™) assay without Wells Criteria. The British Thoracic Society agrees with the recommendation and recommends that SimpliRED™ be limited to low pretest probability groups, i.e., a Wells of less than three.

The ACEP gives a B recommendation for the use of a negative ELISA or turbidimetric D-dimer to rule out PE in the low risk groups only. The ACEP only gives a C recommendation for using the immunofiltration D-dimer because it is new and lacks the data of the other tests. However, BTS has taken the stance of a level B recommendation that any D-dimer in the low risk group can exclude PE, while the VIDAS and MDA D-dimers exclude PE in both low and intermediate risk groups. BTS further recommends that each hospital provide information on the sensitivity and specificity of its D-dimer test. Using the BTS guidelines, it is possible to rapidly rule out a PE in a patient even with intermediate pretest probability, if the hospital has the VIDAS or MDA tests (1, 2).

Alveolar Dead-Space Evaluation

As pulmonary emboli result in an obstruction of the vasculature without affecting airway patency, an increased physiologic dead-space would be expected. This can be quantified by comparing the arterial and expired carbon dioxide levels. The percentage of alveolar dead-space can be calculated by a modification of the Enghoff equation (51):

$$\text{Dead-Space Percent} = 100 \times (P_aCO_2 - P_{et}CO_2) / (P_aCO_2)$$

An abnormal result is generally considered >20%. End tidal CO_2 is available in many EDs at the bedside and can be used for this method, although in the studies analyzing the use of dead-space fraction, measurements were done by respiratory therapists with portable equipment and simultaneous drawing of arterial blood (52).

While this is not useful as a sole test, the combination of a D-dimer and a normal alveolar-dead space percentage may be more sensitive than a D-dimer alone. Kline et al. used this strategy, which yielded a false negative rate of less than 1% (53, 54).

Nuclear Isotope Lung Scanning—Ventilation/Perfusion (V/Q) Scan

In the past, ventilation/perfusion imaging was considered the diagnostic test of choice for the evaluation of PE. PIOPED established the accuracy of this test with a criterion standard of pulmonary angiogram. However, the use of the V/Q scan is problematic, primarily because its interpretation is hindered by multiple cutoffs, ranging from normal to high probability, each with its own diagnostic characteristics. While the PIOPED study established four levels of test reporting—normal, low probability, intermediate probability, and high probability—the low and intermediate results should preferably be referred to as non-diagnostic. More than 60% of patients fell into this non-diagnostic category. In PIOPED, even when the scan was read as normal, there was still a 4% incidence of PE; similarly troubling, high probability scans were associated with a 12% false positive rate. However, other studies have shown that withholding anticoagulation from patients with a normal V/Q scan resulted in a less than 1% subsequent PE on long-term follow-up (55, 56).

The ACEP has made a level A recommendation that patients with low-to-moderate pretest probability and a normal V/Q scan can be deemed not to have a significant PE. However, if the same patients have a non-diagnostic V/Q scan, the ACEP's B level recommendation is that in order to exclude significant PE without going to pulmonary angiogram, the patient must have one of the following: a negative turbidimetric or ELISA assay, a negative whole blood D-dimer with a Wells score less than 4, negative bilateral ultrasound in low probability group only, or negative serial bilateral ultrasound for the moderate Wells score group. The BTS guidelines differ; with a level B recommendation they prefer that a V/Q scan be the initial investigation only if a chest radiograph is normal, there is no concurrent cardiopulmonary disease, standardized reporting criteria are used, and a non-diagnostic result is followed by further imaging. BTS also considers that a normal V/Q scan reliably excludes PE in low risk groups and in intermediate groups with a negative VIDAS™ or MDA™ D-dimer. Thus, while ACEP guidelines state that a V/Q scan cannot rule out PE in a high probability groups, the BTS guidelines conclude that a normal V/Q scan can only rule out PE in a high probability patient if it is read as normal AND the patient has a normal chest X-ray and no baseline cardiopulmonary disease. Otherwise, BTS states that the patient must go on to CT angiogram.

Leg Ultrasound

Doppler examination of the lower extremities can be used to establish the diagnosis of PE if the clinician accepts the proposition that the presence of DVT in a patient with symptoms suggestive of PE confirms a PE. Patients with confirmed PE will have DVT identified by leg ultrasound in approximately 50–70% of cases (14, 55). The treatment for stable PE and DVT is the same, so it may be valuable to use leg ultrasound as an initial test in stable patients with suspected venous thromboembolism (VTE) or after inconclusive imaging. Limiting the use of this test to patients with signs or symptoms of DVT can increase the diagnostic yield. If the clinician has been trained and has the available equipment, a positive bedside ultrasound can quickly and accurately make the diagnosis of DVT and therefore PE (57).

Ultrasound also has implications for the possibility of recurrent PE. Theoretically, if diagnostic testing misses a PE, but there is no more clot to embolize, then the patient will not incur as significant a risk from the misdiagnosis. Serial leg imaging has been found to be useful with a 3-month venous thromboembolism (DVT or PE) rate of only 0.5% among patients with non-diagnostic V/Q scans and initial negative lower extremity Dopplers for DVT (58, 59), but such protocols require reliable patient follow-up and may have resource implications for repeat visits.

The ACEP supports using serial ultrasound for nondeterminate V/Q in low risk groups. BTS recommends the opposite use of ultrasound; a positive ultrasound in patients suspected of having a PE to confirm diagnosis. However, the BTS position is in agreement with the current literature and states that a single leg ultrasound should not be used for exclusion of subclinical DVT.

CT Angiogram

In many institutions, the spiral CT has become the initial diagnostic modality for PE, because of the high number of indeterminate studies obtained using conventional V/Q scans (14). The spiral CT, using as little as 100 cc of contrast, will directly visualize thromboembolic filling defects as well as pleural effusions, vascular remodeling, and oligemia, any of which may be present with PE (60). It is important to note that adequate visualization of the pulmonary vasculature cannot be accomplished with a standard CT scan of the chest; it requires dedicated imaging procedures and protocols often referred to as CT angiogram (CTA). Using CT angiogram as the initial imaging modality has proven to be cost effective (61).

Another advantage of the CTA is that it may reveal alternative diagnoses. A patient suspected of having PE may turn out to have pneumonia, aortic dissection, tumor or pneumothorax, all which can be revealed by the CTA (62).

Historically, the main limitation of spiral CT has been the inability to identify subsegmental PE (63). In the ACEP guidelines, it is noted that the sensitivity of spiral CT for large segmental emboli is greater than 95%, while for subsegmental emboli it is only 77%, according to three studies from 1996–1997 (64–66). A recent review of the spiral CT literature is much more promising (60). In 2000, Goodman (67) showed a 1% rate of PE on follow-up after normal spiral CT. In 2002–2003, two retrospective and two prospective studies were published with enrollments of 993, 441, 507 and 246 respectively (68–71). The studies had a false negative rate of 0.9–1.2% and proved that patient outcome is not adversely affected by withholding anticoagulation on the basis of a good-quality, normal spiral CT.

In 1998, multidetector CT scanners became available; these scanners can image multiple slices with a single revolution of the detectors. Sixteen multidetector spiral CT scanners are now available (60, 72), with the number of detectors growing yearly. The multidetector scanners allow 1-mm to sub-millimeter resolution, and the data can be transformed into 2-D and 3-D reconstructed images. One of the most important features of this new technology is the ability to image the entire pulmonary vasculature in one breath-hold. As a result of these advantages, the multidetector scanners are able to significantly increase the detection of subsegmental PE and evaluate pulmonary vasculature down to 6th-order branches (73–75). PIOPED II, a study of CT scanners for the diagnosis of PE, will further elaborate on the accuracy of the new-generation scanners and test their ability to scan for pelvis and thigh DVT while the patient is receiving the pulmonary scan (76). The latter strategy is referred to as "CT venogram" (CTV). Using the same contrast bolus as the CTA of the chest, DVTs can be detected from the pelvis all the way down to the calves. While it carries the downside of increased radiation dosing, this approach offers increased sensitivity. In a seven-center prospective trial, scanning the pelvis and legs above the knee identified an additional 18% of patients needing anticoagulation (77). However, it is important to note that this study was done in 1998–1999, when the first generation of multidetector CTs first became available (55), and the same machine was not used at all sites. It is possible that the new multidetector scanners would have found pulmonary embolisms in many of the patients who had the sole venogram diagnosis of DVT.

In response to the emerging data on CTA, the ACEP makes a level B recommendation that thin spiral CT with 1–2 mm image reconstruction may be used as an alternative to V/Q scan during the diagnostic evaluation of the patient with suspected PE, and a C recommendation to also perform CT venogram. The BTS guidelines place an even greater faith in the use of CTA for the diagnosis of PE. With a level B recommendation, they state that the CT pulmonary angiography is the recommended imaging modality for non-massive PE. Furthermore, BTS has stated that patients with a good quality CT angiogram need no further investigation for PE regardless of the assigned level of pretest probability.

Echocardiography

Bedside echocardiography will demonstrate evidence of PE in up to 80% of cases (78), especially in unstable patients when transesophageal echo (TEE) is used (79). Intracardiac thrombi in the right heart may also be visualized. Echocardiography is especially useful for patients suspected of massive PE or unstable patients who cannot be moved safely outside of the ED. Furthermore, patients with right ventricular dysfunction may benefit from the administration of thrombolytic therapy.

Conventional Angiogram

The pulmonary angiogram was long considered ideal for diagnosis of PE. The test is no longer even available at some centers, and radiologists who were once facile with the process now perform and interpret these scans only rarely. Even when it was used commonly, there was a high rate of interobserver disagreement for subsegmental PEs (80). The test used today is often digital subtraction angiography (DSA); it is unknown whether the conventional angiography sensitivities are still applicable (81). The accuracy of the conventional pulmonary angiogram relies on selective catheterization of each subsegmental branch of the pulmonary vasculature. Angiography of only segmental branches, a common way of performing the exam, will lower the sensitivities (82).

The recurrence rate of pulmonary embolism in patients with normal angiograms ranges from 0.6–4.2% (83). Serious complications (from dye load, renal nephropathy and the invasive nature of the procedure) occur in 1.5% of cases, and a 0.5% procedural mortality rate has been reported (15). However, newer generation CT scanners appear to produce similar if not better results with less invasive risk. Data from PIOPED II will establish whether CTA should be the new criterion standard for pulmonary embolism.

Post-test Probability

After testing, a post-test probability can be generated. If this probability crosses the threshold for "ruling-in" or "ruling-out" the diagnosis of PE, then the evaluation is complete. However, if diagnostic uncertainty still exists, the patient will have to undergo further evaluation using the generated post-test probability as the new pretest probability. Whether this testing will take place in the ED, on the inpatient ward, or at a later follow-up appointment depends on the individual clinical situation.

Treatment

While the diagnosis of PE is a true test of clinical acumen, the treatment is relatively straightforward. Countless review articles and monographs discuss the treatment regimens for venous thromboembolism (e.g., 12, 13, 25). Areas of new interest include the use of low-molecular-weight heparin and indications for the use of thrombolytics.

Low-Molecular-Weight Heparin

Anticoagulation must be administered to patients with confirmed PE. For unstable patients or those at high risk, anticoagulation is often administered empirically while the patient is undergoing further workup. This may be achieved with equal efficacy by using either low-molecular-weight heparin (LMWH) or unfractionated heparin (84–86). Unfractionated heparin will have a quicker onset and, according to BTS, may be more desirable for massive PE or any situation in which anticoagulation may need reversal.

LMWH does not require monitoring of partial thromboplastin time (PTT), is accurately dosed on a per kilogram basis in a once or twice daily fashion, and is less likely to induce bleeding and thrombocytopenia. Low-molecular-weight heparins seem ideally suited to the environment of the ED when infusions require medication pumps and careful nursing care, and one subcutaneous injection allows twelve hours without any further treatment administration.

Low-molecular-weight heparins also offer the additional flexibility of treatment in the patient's home. For stable patients with confirmed pulmonary embolism, the strategy of discharge with follow-up and prescription for LMWH can be considered. At this point, the data is still accumulating, but this strategy may allow outpatient management of a disease that prior to now uniformly required hospital admission. Sending patients with non-diagnostic work-ups home on LMWH is also a tenable option. Patients would be able to stay on treatment until follow-up testing sufficiently lowers the possibility of PE. However, further studies must be performed before this strategy can be recommended.

Thrombolysis

If a massive PE causes circulatory collapse, early thrombolysis is recommended (87). One study in a controlled trial of thrombolysis versus heparin was aborted after 4 patients who were given thrombolytics lived while 4 patients given only heparin died

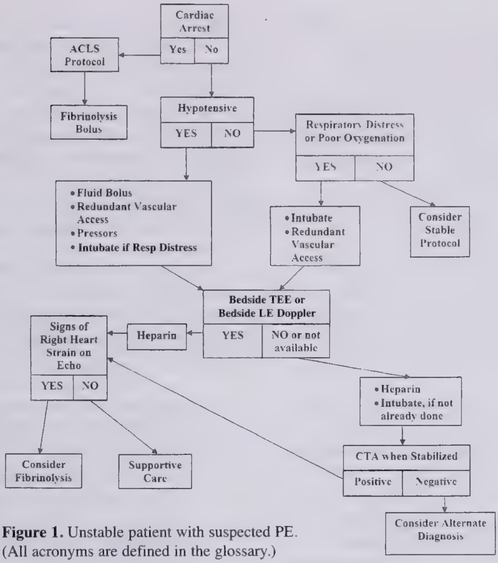
Cardiac Arrest
Yes
No
ACLS Protocol
Fibrinolysis Bolus
Hypotensive
YES
NO
Respiratory Distress or Poor Oxygenation
YES
NO
• Fluid Bolus
• Redundant Vascular Access
• Pressors
• Intubate if Resp Distress
• Intubate
• Redundant Vascular Access
Consider Stable Protocol
Bedside TEE or Bedside LE Doppler
YES
NO or not available
Heparin
Signs of Right Heart Strain on Echo
YES
NO
• Heparin
• Intubate, if not already done
CTA when Stabilized
Positive
Negative
Consider Fibrinolysis
Supportive Care
Consider Alternate Diagnosis

Figure 1. Unstable patient with suspected PE. (All acronyms are defined in the glossary.)

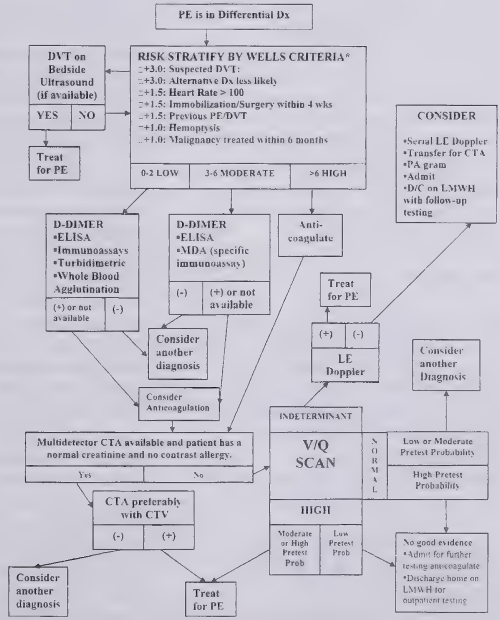
PE is in Differential Dx
RISK STRATIFY BY WELLS CRITERIA*
☐+3.0: Suspected DVT:
☐+3.0: Alternative Dx less likely
☐+1.5: Heart Rate > 100
☐+1.5: Immobilization/Surgery within 4 wks
☐+1.5: Previous PE/DVT
☐+1.0: Hemoptysis
☐+1.0: Malignancy treated within 6 months
0-2 LOW
3-6 MODERATE
>6 HIGH
DVT on Bedside Ultrasound (if available)
YES
NO
Treat for PE
CONSIDER
•Serial LE Doppler
•Transfer for CTA
•PA gram
•Admit
•D/C on LMWH with follow-up testing
D-DIMER
•ELISA
•Immunoassays
•Turbidimetric
•Whole Blood Agglutination
(+) or not available
(-)
D-DIMER
•ELISA
•MDA (specific immunoassay)
(-)
(+) or not available
Anti-coagulate
Consider another diagnosis
Consider Anticoagulation
Treat for PE
(+)
(-)
LE Doppler
Consider another Diagnosis
Multidetector CTA available and patient has a normal creatinine and no contrast allergy.
Yes
No
INDETERMINANT
V/Q SCAN
NORMAL
Low or Moderate Pretest Probability
High Pretest Probability
HIGH
Moderate or High Pretest Prob
Low Pretest Prob
CTA preferably with CTV
(-)
(+)
Consider another diagnosis
Treat for PE
No good evidence
•Admit for further testing anticoagulate
•Discharge home on LMWH for outpatient testing

Figure 2. Stable patient with suspected PE. (All acronyms are defined in the glossary.)
*May also use other objective criteria (Wicki or Kline)

Key Concepts

1. PE should be considered in any patient with unexplained dyspnea, tachypnea or chest pain. These patients must be risk stratified, ideally by a clinical decision rule.
2. A negative ELISA or MDA™ D-dimer will exclude PE in both low- and moderate-risk groups. Turbidimetric and SimpliRED™ D-dimers will exclude PE in low-risk groups. Latex agglutination D-dimers should not be used for excluding PE in any group. An alternative diagnosis should always be sought when PE is excluded.
3. CT angiogram (CTA) with a multidetector scanner is the initial imaging study for stable patients with suspected PE. For patients with low and moderate clinical pretest probability, a negative CTA excludes the diagnosis of PE.
4. V/Q scans should be used only when CTA is not available or contraindicated. All indeterminate scans should have a CTA or pulmonary angiogram done before PE is excluded.
5. Unfractionated heparin and low-molecular-weight heparin are both treatment options for patients with PE. In patients with confirmed PE and hypotension, thrombolytics should be administered if not contraindicated.

(88). Currently, clear data exist only for lysis in hypotensive patients (87–91). Debate is ongoing as to whether stable patients with right ventricle strain on echocardiogram should receive thrombolysis. Patients with right heart strain who received thrombolysis recovered right heart function more rapidly, but there was no demonstrated mortality benefit (92–95).

While the BTS supports a C recommendation of using alteplase (96) for fibrinolysis of PE because it does not worsen hypotension, currently the FDA has approved the use of streptokinase, urokinase or rt-PA for the treatment of pulmonary embolism. The ACEP gives a level B recommendation to considering thrombolytics in hemodynamically unstable patients with proven PE, and a C recommendation to the lysing of unstable patients with high clinical suspicion of PE. The ACEP also gives a level C recommendation for fibrinolysis of stable patients with confirmed PE and right ventricular dysfunction on echocardiography.

Conclusions

Diagnosis of PE may again change when the results of PIOPED II are published. In the interim, the ACEP clinical policy and BTS guidelines give an evidence-based roadmap to the evaluation and treatment of pulmonary embolism. The following are key points to the approach to pulmonary embolism in the emergency department:

1. We should consider PE in any patient with unexplained dyspnea, tachypnea, or chest pain.
2. All patients suspected of PE must be risk stratified, ideally by using criteria validated by a clinical decision rule.
3. If both PE and DVT are suspected and ultrasound is readily available, a positive leg ultrasound for DVT is sufficient for the diagnosis of pulmonary embolism, and treatment should be initiated.
4. If the VIDAS™ or MDA™ D-dimer is negative, PE may be excluded in the low- and moderate-risk groups. Other D-dimer assays (ELISA, turbidimetric, SimpliRED™) will reliably exclude PE in the low-risk group and no further imaging is warranted.
5. CT angiogram is the initial imaging study of choice for stable patients. In patients with low- and moderate-pretest probability, a negative CTA effectively excludes the diagnosis of pulmonary embolism.
6. V/Q scans should be used only when CT is not available or the patient has a contraindication to CT scans or intravenous contrast. If V/Q is normal, another diagnosis should be sought. Patients with indeterminate V/Q scans should have CT angiogram performed. Patients with indeterminate scans in the high probability group should receive CTA or pulmonary angiogram. Patients in the moderate- and low-risk groups with indeterminate scans can have PE excluded by serial leg ultrasounds.
7. Bedside echocardiography or hemodynamic status of the patient and CT angiogram are used diagnostically for suspected massive PE. If PE is confirmed, hypotensive patients should be given lysis. For hypotensive patients with high clinical suspicion of PE, thrombolytics can be considered.
8. Unfractionated heparin and low-molecular-weight heparin are both treatment options for patients with confirmed pulmonary embolism.
9. The diagnostic algorithms represented in Figs. 1 and 2 provide a stepwise approach to both

the stable and unstable patient with respect to the current data presented in this paper.

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Blunt Cardiac Injury

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Abstract

The diagnosis and management of blunt cardiac injury, formerly known as myocardial contusion, has challenged clinicians for decades. Caused primarily by motor vehicle collisions, significant blunt cardiac injury carries a high mortality rate. Yet no reliable diagnostic test exists to identify those patients at greatest risk for an adverse outcome. A literature search using the MEDLINE database was performed to compose a review of epidemiology, diagnostic intervention, and therapeutic approach.

The results of the search indicate that, along with a high index of suspicion, utilizing a combination of electrocardiogram, troponin, and echocardiography for appropriate patients may improve the diagnosis, risk stratification and disposition of patients sustaining blunt cardiac injury.

Key Words: Myocardial contusion, myocardial concussion, myocardial rupture, blunt cardiac injury, pericardial tamponade, blunt trauma, echocardiography, pericardiocentesis, cardiogenic failure.

Introduction

THE TERM "BLUNT CARDIAC INJURY" (BCI) describes a spectrum of myocardial lesions acquired from non-penetrating mechanisms. Sequelae from these injuries range from the benign to catastrophic. Traumatic injuries remain the fifth leading killer of Americans (1). It has been estimated that in the prehospital setting, 20% of traumatic deaths are caused by cardiac-related injuries (2). Over the past 2 decades, the improvement of prehospital transport and early implementation of advanced life support (ALS) have enabled victims of formerly nonsurvivable cardiac injuries to arrive in advance of terminal shock. A heightened level of suspicion and early identification of the blunt cardiac injury is vital. Reliable detection, however is challenging, as there are still no diagnostic criteria for blunt cardiac injury (3).

Nomenclature

Historically, the term "myocardial contusion and concussion" was criticized for its lack of specificity for severity and injury pattern. "Myocardial contusion" was used as a general term encompassing the gamut of myocardial injuries. The true incidence of myocardial injury is difficult to discern, since studies differ in their diagnostic criteria. The reported incidence of myocardial contusion ranges from 17 – 70% in different study populations despite similar mechanisms of injury (2, 3). The interpretation of literature using these terms remains problematic and fails to assist in the identification of patients at greatest risk. In 1992, Mattox recommended the replacement of "myocardial contusion and concussion" with "blunt cardiac injury" along with specific descriptors to provide less ambiguous identification of the injury and its sequelae (Table) (3).

The following review presents an evidence-based approach to the evaluation and management of the patient who presents with blunt thoracic injury that may involve a cardiac injury.

Epidemiology

The Centers for Disease Control and Prevention (CDC) reports that approximately 30,000 pa-

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TABLE
Types of Blunt Cardiac Injury (3)

Blunt cardiac injury with minor ECG or enzyme abnormality
Blunt cardiac injury with complex arrhythmia
Blunt cardiac injury with coronary artery thrombosis
Blunt cardiac injury with free wall rupture
Blunt cardiac injury with septal rupture
Blunt cardiac injury with cardiac failure

Copied with permission from Mattox KL, Flint LM, Carrico CJ, et al. Blunt cardiac injury. J Trauma 1992; 33(5):649–650 (3).

tients per year with a diagnosis of BCI survive to discharge (4). While a majority of cardiac injuries are sustained during motor vehicle collisions (MVC), falls, blast injuries, and other blunt mechanisms have also been described (2, 5). The contused myocardium is characterized by muscle necrosis, edema, and hemorrhagic infiltrate. Outcomes vary from asymptomatic electrocardiographic changes to cardiogenic shock and death.

The spectrum of injuries is dependent upon the mechanism and degree of force (2, 5). Parmley et al., in a 1956 autopsy study of 546 non-penetrating cardiac trauma cases, found that 64% had at least one chamber rupture, 20% had two or more, 23% had a myocardial contusion, 6% had pericardial lacerations, 4% had a papillary muscle rupture, 2% had a valvular rupture, and 1% had a coronary artery laceration (2). The authors describe 7 categories of force resulting in cardiac injury: (a) direct, (b) indirect, (c) bidirectional or compressive, (d) decelerative, (e) blast, (f) concussive, and (g) combined (2). Direct, compressive, decelerative, and concussive forces are discussed below.

Direct precordial impact and crush injuries result from compression between the sternum and spine. Injuries to the pericardium, myocardium and coronary vessels are characteristic (2, 6). The compressible thoracic and abdominal cavities are adjacent to the heart. Forceful, abrupt pressure fluctuations in these compartments can be distributed to the heart, resulting in tears to its structural walls and valves (2, 6, 7). Because the heart is a dynamic organ, movements in the chest cavity are exaggerated during deceleration, causing the heart to strike rigid structures and forcefully tear itself from its static attachments. The aortic attachments, as well as regions between the atria, pulmonary vessels and the vena cava, are especially vulnerable (2, 6).

Concussive force tends to be of low magnitude and is not associated with pathologic lesions to the myocardium or its vessels (2). Further discussion on concussive force is found in the section "Blunt Cardiac Injury with Complex Arrhythmia." Finally, penetrating cardiac lesions, despite blunt mechanism, may result paradoxically from closed thoracic injuries secondary to fractured ribs or sternum (6, 8). Blunt cardiac injuries, by virtue of the degree of force, present with coexisting injuries. In order of frequency, the following injuries have been shown to be associated with BCI: head injury, rib fracture, extremity injury, hemothorax, sternal fracture, pulmonary contusion, aortic or great vessel injury, pneumothorax, abdominal injuries, and flail chest (9).

Approach to the Patient with Suspected Blunt Cardiac Injury

Cardiac injury can be missed due to concomitant bodily injuries. Patients with neurologic, multiple extremity or organ injuries are especially at risk, as their manifestations can mask those of the injured heart. A high index of suspicion and proper triage is essential.

History

Determine whether the presenting trauma patient has sustained a thoracic injury. MVC patients should be asked specifically whether restraints were used and if there was steering wheel impact to the chest. The most common presenting symptom is chest pain. Assess if there are any cardiac risk factors, including prior myocardial infarction (MI), recent angioplasty or stress test, angina, hypertension, hypercholesterolemia, tobacco use, cocaine use, or family history of early death secondary to an MI. Document medications, particularly beta-blockers or calcium channel blockers, which may alter findings on clinical examination; for example, by masking tachycardia.

Physical Examination

Perform a thorough physical examination with emphasis on vital signs, head and neck, lungs, and heart. Suggestive of cardiac injury are findings of hypotension, jugular venous distension (JVD), tachypnea, wheezing, rhonchi, chest abrasion or ecchymosis, imprints of a seatbelt or steering wheel, chest tenderness, palpable crepitus, flail chest, fractures of the rib(s), sternum or clavicle , distant heart sounds, S3, tachycardia, bradycardia, rub or murmurs. Pulsus paradoxus (excessive decline of systolic pressure during inspiration) is diagnostic of cardiac tamponade (10).

Initial Stabilization

Ensure that the patient has a patent secured airway, supplemental oxygen, adequate intravenous access, and continuous cardiac monitoring. A chest X-ray and ECG are compulsory for the blunt throracic patient (11). If the patient has underlying risk factors for cardiac disease or is over the age of 65 and complaining of chest pain or discomfort, cardiac troponin levels can be obtained (11). If the patient is unable to provide an adequate history or exam, presume that a cardiac injury exists. A Focused Assessment of Sonographic Trauma (FAST) exam should be performed if there is an available ultrasound, with special attention given to the evaluation of the pericardium (12).

Diagnostic Intervention

In the absence of an ideal set of diagnostic criteria, perioperative visualization and autopsy remain the sole methods of reliably diagnosing a myocardial contusion. A number of tests have been used to screen for pathology and stratify patient severity.

Chest Radiography

The standard work-up for all thoracic trauma patients should include a chest X-ray. X-rays lack sensitivity and specificity for cardiac injury. They do however identify other injuries, including aortic disruption, rib or sternal fractures, pulmonary contusions, hemothorax and pneumothorax, all of which are associated with BCI (5, 13).

Electrocardiogram

The electrocardiogram (ECG) is a rapid, inexpensive bedside study, and should be performed on all patients for whom BCI is suspected (11). Foil et al., in a retrospective evaluation of 524 blunt chest trauma patients, found that 85% of the patients with complications (mostly arrhythmias) had an abnormal admission ECG (14). In a retrospective analysis of 359 patients with blunt chest trauma, Biffl et al. identified an abnormal admission ECG (excluding sinus tachycardia) as the most significant independent predictor of a complication, defined as dysrhythmia requiring intervention, cardiogenic shock, valvular rupture, or pericardial tamponade (15). Maenza et al., in a meta-analysis of 43 studies, noted that an abnormal ECG correlated with the risk of developing a complication from BCI (16). In a multicenter review of 184 pediatric BCI patients published by the Pediatric Emergency Medicine Collaborative Research Committee, no hemodynamically stable patient with a normal ECG developed cardiac complications (17). Several studies have concluded that hemodynamically stable patients with normal ECGs require no additional studies (14, 18, 19). Feghali and Prisant, in a review of 35 BCI articles, concluded that ECG has a good negative predictive value (20).

There are no prototypical ECG findings that are specific for BCI. Fifty per cent of admission ECGs have nonspecific findings (9). However, when all ECG changes (including tachycardia and nonspecific changes) are included in the BCI work-up, the sensitivity of ECG for diagnosing BCI approaches 96%, with a specificity of 47% (21, 22). The most common finding is sinus tachycardia, followed by premature atrial or ventricular contractions (PAC, PVC). Other abnormalities in order of frequency include: T wave changes, atrial fibrillation/flutter, ST elevation or depression, conduction delays, ventricular dysrhythmias and new Q waves. Of all arrhythmias requiring an intervention, 80% are detected on emergency department (ED) admission (23).

Patients with normal admission ECGs have been reported to have delayed presentations of cardiac injury. These patients are typically elderly and have pre-existing cardiac disease, multiple severe chest wall injuries or unexplained hypotension (14, 15). Fildes et al., based on a prosective evaluation of 100 patients admitted to rule out myocardial injury, recommend that hemodynamically stable patients with no history of cardiac disease, who are less than 55 years old and do not require surgery or observation for other injuries can have a diagnosis of cardiac contusion excluded if there is a normal admission ECG. Patients with abnormal ECG should have at least 24 hours of cardiac monitoring and a follow-up ECG (24).

Cardiac Enzymes

The pathophysiology of trauma-induced myocardial necrosis is poorly understood. It is therefore difficult to predict the pattern of myocyte enzymatic release, and it remains unclear whether a role exists for its routine measurement. Historically, creatine kinase (CK) with myocardial type B (MB) fractions were utilized in order to assist in the detection of BCI or patients at risk for serious sequelae. Healey et al., in a retrospective evaluation of 342 BCI patients, found that a CK-MB level of >200 mg/dL had a 100% positive predictive value for cardiac complications (22). In contrast to the findings by Healey et al., a preponderance of the literature suggests that CK-MB is not predictive of complications and is not a warranted study (11). CK-MB has been isolated in skeletal muscle, lung, stomach, pancreas, liver, small intestine, and colon (25). The release of CK-MB from other organs during trauma can potentially confound the interpretation of the value. In a retrospective analysis of 133 patients, Illig et al. found that CK-MB analysis failed to predict complications secondary to BCI (26). In a retrospective review, Biffl et al. later confirmed this finding in a series of 359 patients. None of the BCI patients who went on to have complications had cardiac enzyme abnormalities (15).

The advent of the cardiac-specific troponin I poses an opportunity to selectively screen patients with BCI. Troponin I is found only in the cardiac myocyte and interacts with the actin-myosin complex. In a recent study, Relos et al. concluded that even moderate elevations in serum troponin I were indicative of myocardial injury and predictive of a 4-fold mortality increase in surgical patients (27). Troponin I in BCI patients has a sensitivity of 23–100% and a specificity of 85–97% (28–30). In a small, prospective pediatric series, 4 patients were diagnosed with BCI on the basis of history combined with abnormal echocardiographic findings and ECG abnormalities: 3 of these 4 patients had elevated troponin I levels of > 2.0 ng/mL (31). In a prospective review of 333 blunt thoracic patients, Velmahos et al. identified 13% with significant BCI, defined as hypotension in the absence of bleeding or neurogenic cause, cardiac arrythmias, post-traumatic echocardiographic abnormality, or cardiac index <2.5. By combining the ECG and troponin I at 8 hours, a negative predictive value of 100% was rendered, eliminating patients without significant BCI. The authors concluded that in the absence of other injuries or hemodynamic instability, patients with normal ECG and troponin I can be discharged (32).

Echocardiogram

Echocardiography plays a significant role in the work-up of the BCI patient. It is the primary exam in the structural assessment of the heart. Up to 30% of BCI patients have abnormal echocardiographic findings (33). Detection of pericardial effusion, myocardial contusion, valvular disruption and wall motion abnormalities may assist in defining injury severity and potentially alters management. Non-cardiac lesions such as pleural effusion, intracardiac thrombi, and aortic disruptions may also be identified by this means.

In the past decade, the bedside Focused Assessment with Sonography for Trauma (FAST) exam has increasingly become standard in US trauma centers (34). This noninvasive bedside sonographic exam can be performed accurately by trained emergency physicians and surgeons (12, 34). Four sonographic windows placed in the subcostal, right upper quadrant, left upper quadrant, and suprapubic areas detect the presence of significant amounts of free fluid. The speed of the exam was validated in a study by Sisley et al., who demonstrated that it could be completed in an average of 1.3 minutes (35). The pericardial window allows ample visualization of the pericardium and heart, to rule out pericardial effusion and tamponade. The use of the parasternal long axis, apical four chamber, and subcostal windows (used in the FAST) provides multidimensional views of the pericardial sac. Mandavia et al. concluded that, using these views, emergency physicians could reliably examine the pericardium with an accuracy of 97.5% (12). Rozycki et al. conducted a study of 247 penetrating chest injury patients, demonstrating a 100% sensitivity and specificity for hemopericardium with the use of FAST (36). In a separate multicenter study, Rozycki et al. utilized FAST to minimize ED to operating room (OR) times to an average of 12.1 minutes (37).

Formal echocardiography has proven to have great diagnostic utility for the unstable or complicated BCI patient (23, 38). Applications such as M-Mode and Doppler provide additional information not recognized on the limited FAST exam. Abnormalities such as wall motion defects and valvular incompetence are readily recognized. Echocardiography, however, lacks utility for the stable BCI patient. Karalis et al., in a prospective analysis of 105 patients, concluded that routine echocardiograms were of no value, for them, since there were few cardiac complications secondary to BCI (39). Nagy et al., in a prospective analysis of 315 patients, ascertained that the echocardiogram had no added diagnostic utility for patients with normal ECG and blood pressure on admission (19). In a meta-analysis of 18 studies of patients suspected of myocardial contusion, Christensen and Sutton concluded that there is no evidence to support the use of routine echocardiography. However, echocardiography maintains its value in detecting multiple structural abnormalities, e.g., apical thrombi, pericardial effusions, and pump failure in patients deemed to be at increased risk or suffering from a complicated in-patient course (23). In a prospective study of 118 blunt trauma patients, Lindstaedt et al. identified 14 patients (11.8%) with myocardial contusion diagnosed by an abnormal echocardiogram, defined as new akinetic or dyskinetic regional wall abnormalities. Other than a mural thrombus found on a 12-month follow-up, Lindstaedt found that none of these patients developed cardiac complications over the course of 1 year (40). Bromberg et al. similarly demonstrated, in a series of 8 children with BCI, that echocardiography was only valuable for patients who developed cardiac complications (41). Thus, echocardiography should be reserved as a complementary rather than primary screening tool for BCI. The Eastern Association for the Surgery of Trauma recommends selective use of echocardiography for patients who are hemodynamically unstable or suffer cardiac complications (11, 42, 43).

The use of transthoracic echocardiography (TTE), however valuable, may prove challenging to perform in the presence of severe chest wall injuries, pleural tubes, mechanical ventilation, and large body habitus. Karalis et al. found in his study of 105 blunt chest trauma patients, that TTE was useful for 80% of patients, yet 19% had suboptimal studies (39). Alternatively, the transesophageal echocardiogram (TEE) may be utilized. TEE, in contrast to TTE, is invasive and requires sedation and possible intubation. However, it has the added benefit of increased resolution and ability to detect thoracic aortic injuries. Chirillo et al. found that although 98% of blunt chest trauma patients successfully underwent TEE, TTE was feasible in only 38% (44). Moreover, both Chirillo and Weiss, in their respective series, concluded that TEE accurately identified evidence of contusion and valvular injuries that were missed by TTE (44, 45).

Pericardiocentesis

Pericardiocentesis, as a diagnostic modality, has virtually been supplanted by the use of ultrasound. However, lack of equipment or radiology personnel may render pericardiocentesis the exam of preference to rule out suspected tamponade. Blind insertion of the needle into the pericardial sac has been associated with misleading results 25% of the time. False positives result from the aspiration of blood directly from the cardiac chamber. False negatives result from the immediate clotting of aspirated blood from a rapidly bleeding laceration (46). ECG or sonographic guidance using the subxiphoid approach is recommended (47).

The patient in cardiac tamponade benefits from emergency pericardiocentesis. Inserting a drainage catheter may delay reaccumulation of blood in the pericardial sac, although it may clot. The procedure temporizes the condition until surgical intervention can be arranged (47).

Emergent Thoracotomy

Prompt emergency department thoracotomy in the cardiac-arrest blunt trauma patient has been documented to carry a 0–16% survival rate. Associated mitigating factors in survival include the identification of a cardiac injury or the presence of pupil reactivity, voluntary respiratory efforts, or purposeful movement upon ED admission (48, 49). Blunt trauma patients who arrest in the prehospital setting are not candidates for ED thoracotomy. In the event that pericardiocentesis is unsuccessful, the patient's vital signs deteriorate, or cardiac arrest ensues in the ED, thoracotomy and pericardiotomy are indicated (50). A left lateral incision is used to access the heart and clamp the descending aorta. If necessary, the lateral incision may be extended across the midline and sternum, creating a "clam shell" incision. This allows ample access to the right heart. Pericardiotomy should be performed with a parallel incision to the phrenic nerve. Once the clot has been removed, the site of injury should be identified. Atrial hemorrhage is occluded using digital pressure, a clamp, or an inflated foley catheter. Ventricular hemorrhage may be controlled similarly, with digital pressure or standard skin staples. Bimanual cardiac compressions should ensue immediately once the source of injury is stabilized (47).

Pulmonary Artery Catheter

The use of the pulmonary artery catheter, though invasive, has distinct value in the evaluation of the critical BCI patient. Evidence of hemodynamic instability, age greater than 60, abnormal ECG, and future surgical intervention under general anesthesia have been described as rationales for its insertion (21). Unlike the echocardiogram, the catheter provides continuous, precise information regarding preload, afterload, and ventricular function. These parameters may serve an essential role during the resuscitation of the multisystem-involved volume-depleted patient with heart failure or pulmonary hypertension (21).

Blunt Cardiac Injury with Minor ECG or Enzyme Abnormality

Patients with isolated ECG or enzyme abnormality represent the largest and most benign subset of BCI patients. However, the existence of ECG and/or cardiac enzyme abnormalities in BCI has been correlated with clinically significant outcomes. In a retrospective meta-analysis of 2,210 BCI patients, Maenza et al. found that the existence of a positive ECG or a cardiac enzyme abnormality correlated with an increased risk of an operative or cardiac intervention (16). In another study, Velmahos et al. evaluated 333 admitted blunt thoracic trauma patients with serial troponin and ECG at admission, 4 hours, and 8 hours. They reported that 34% of patients diagnosed with ECG *and* enzyme abnormalities had hypotension, cardiac arrhythmias, echocardiographic abnormalities, or low cardiac index <2.5. Moreover, no patient with a normal ECG and negative enzyme abnormality developed BCI (32).

Despite potential acute complications, abnormalities documented upon admission typically resolve within hours, and the patient rarely suffers long-term functional sequelae (51, 52). BCI with minor ECG and/or enzyme abnormality should receive telemetry monitoring and may require further diagnostic testing, including a formal echocardiogram. Intensive care unit (ICU) admission should be reserved for patients with associated hemodynamic instability (53).

Blunt Cardiac Injury with Complex Arrhythmia

Arrhythmias represent the most common complication associated with BCI (16). Up to 70% of patients with BCI will suffer from a rhythm disturbance. The most common arrhythmias are atrial, followed by ventricular, and conduction delays. Atrial or ventricular dysrhythmias requiring an intervention have been documented to occur in up to 30% of patients (9). However, Maenza et al. found, in their meta-analysis, that only 2.6% of BCI patients developed complex cardiac arrythmias requiring an intervention (16). Treatment options include antiarrhythmics and/or electrical cardioversion (1, 9).

Myocardial concussion, commotion or commotio cordis, originally described in 1879, is caused by a direct low impact blow to the chest resulting in an isolated dysrhythmia, syncope, or sudden death (54, 55) . It is characterized as a sudden disturbance of cardiac rhythm in the absence of significant structural damage to the myocardium (54). A majority of patients sustaining such injuries are children who are injured during sporting activities or "play fighting" (55). The electrophysiologic outcome of the injury is dependent upon the timing of impact during the cardiac cycle. Link et al. developed an experimental model that produced ventricular fibrillation when chest wall impacts occurred during a 15 and 30 ms interval preceding the T wave. Impacts during ventricular depolarization were associated with a brief period of heart block. Left bundle branch blocks and ST-T segment changes were also described to correlate with impact timing (56).

Ventricular fibrillation is thought to be the etiology of sudden death in myocardial concussion patients. In one retrospective analysis of 128 confirmed cases of commotio cordis, there was an 84% mortality rate. Selection bias is inherent in this study, since cases were obtained from a national registry of voluntarily submitted cases, a majority involving the death of a minor (55). The implementation of prompt CPR and pre-hospital automatic external defibrillator (AED) use has been shown to increase the survival rate (57, 58).

Blunt Cardiac Injury with Cardiac Failure

Patients with cardiac failure represent approximately 2–20% of patients with identified BCI (9). Contusions cause cellular necrosis and inflammatory changes, which alter ventricular compliance and decrease coronary perfusion (2). Valvular incompetence, pump failure, complex arrhythmias and coronary artery occlusion also compromise cardiac output, thereby causing hypotension (9). The clinical findings that may alert the clinician include hypotension, tachycardia, tachypnea, jugular venous distension, rales, and/or a systolic murmur. Critical care monitoring may reveal an elevated central venous pressure, an abnormal pulmonary artery wedge pressure and low cardiac index (21). Pericardial tamponade may present with similar findings and must be considered in the evaluation of these patients.

The use of echocardiography and pulmonary catheterization may prove instrumental in identifying the source of hemodynamic perturbations and the chamber involved (21).

ICU admission and symptomatic management with intubation, crystalloid, vasopressors, and inotropes are management options. Patients in acute failure associated with hypoxemia should be promptly intubated. This should be followed by crystalloid boluses of 20 cc/kg to correct blood pressure and cardiac index (CI) if the central venous pressure is less than 10. Inotropes such as dobutamine or milrinone should be administered to maintain a CI > 2.2 (59). If blood pressure remains low, vasopressors should be added to elevate to a systolic blood pressure (SBP) of 90. Avoid diuretics, since this may decrease intravascular volume needed to maintain the cardiac output.

Refractory cardiogenic failure has been successfully managed with intra-aortic balloon counter pulsation (IABP), according to case reports. The device decreases left ventricular afterload and increases coronary blood flow, thereby improving left ventricular function. This enables stunned myocardium to return to reasonable parameters in a period of several days to several weeks. IABP is contraindicated in aortic insufficiency (58, 60).

Key Concepts

- All patients with thoracic trauma must have an ECG
- Maintain a high level of suspicion of BCI for patients with chest pain, rib or sternal injuries, pulmonary lesions, or deceleration injury
- Rule out all hypotensive BCI patients for pericardial tamponade by echocardiography
- The risk of significant BCI is insignificant in stable patients with normal ECG and troponin
- Suspect BCI in the multisystem-injured patient with refractory hypotension

ECG = electrocardiogram; BCI = blunt cardiac injury.

Blunt Cardiac Injury with Wall Rupture

Abrupt compressive force to the torso can generate markedly elevated transthoracic and venous pressures. These pressures are transmitted from the neighboring thoracic and abdominal compartments to cardiac chambers and closed valves. The heart chambers are most susceptible to injury when at maximal filling. Although the right heart is most often involved, both ventricles may be ruptured. Ruptures can be either immediate or delayed (6). Paradoxical penetrating lesions with a fractured rib or sternum have been implicated in right atrial and ventricular ruptures (6, 8).

Chamber wall rupture carries the highest mortality rate of the BCI categories. In clinical trials the incidence of chamber rupture is 0–30%, compared to a 64% incidence in autopsy studies (9). More than one chamber will be involved in 20% of the cases (61). Clinical characteristics and outcome depend on the chamber involved and the integrity of the pericardium. In two series of patients with traumatic cardiac rupture, Mattox et al., and Shorr et al., reported 85% and 100% mortality rates, respectively (62, 63). Although, a majority of these patients expire in the prehospital setting, up to 7% of patients have been documented to survive longer than 30 minutes (2). This finding supports the importance of trauma systems with rapid transport capabilities. Rupture of a low-pressure chamber, delayed rupture of a high-pressure chamber, or small, contained pericardial tears may allow the patient to survive transport to the hospital (64). Survival is most common with right atrial rupture (65).

Approximately 70% of patients with cardiac wall rupture develop pericardial effusion and tamponade (46). Extracardiac hemorrhage in excess of 200 cc may render these conditions fatal. When the accumulation of blood exceeds the compliance of the pericardium, intrapericardial pressure rapidly increases, causing collapse of the ventricle, restricting its filling. Getz et al. describe signs of distended neck veins, persistent hypotension, hemothorax, or metabolic acidosis unresponsive to fluid resuscitation as commonly associated with myocardial rupture (46). However, coexistent injuries to other organ systems may mask classic clinical presentations of tamponade because of massive blood loss or neurogenic shock.

The finding of pulsus paradoxus on examination or diastolic ventricular collapse in the setting of pericardial effusion on echocardiogram is pathognomic for tamponade physiology. ECG may demonstrate electrical alternans, in which the QRS complex alternates voltage from beat to beat. Pulmonary artery catheter placement will demonstrate equalization of right and left ventricular pressures (10). Smaller volumes of pericardial fluid and chronic inflammatory effusions may be asymptomatic and initially undetectable. These can collect and may be visualized on subsequent echocardiographic studies (7).

Once the diagnosis is made, emergent pericardiocentesis and/or transport to the OR for a pericardial window must be expedited, since the natural course of this disease is rapidly progressive and deadly. In the event of cardiac arrest or hemodynamic decline refractory to pericardiocentesis, emergent thoracotomy and pericardiotomy is indicated (48, 49).

Septal ruptures may present with cardiac failure with left to right shunt (66). The cardiac valves are at greatest risk for rupture during periods of closure in the cardiac cycle. The most common valves involved are the aortic and mitral valves. The aortic valve is under greatest tension during early diastole, when the left ventricle is empty. The mitral valve is most vulnerable during early systole in isovolumetric contraction. Valvular rupture occurs in up to 6% of BCIs (67). Disruption causes regurgitation and cardiogenic failure that is evident immediately or within weeks. In contrast, insufficiency secondary to a tricuspid or pulmonary rupture is typically asymptomatic for several years (68). Coordination of trauma and cardiothoracic specialist care should not be delayed in cases of BCI with valvular, free wall, or septal rupture.

Pearls and Pitfalls in BCI

Case 1

A 68-year-old driver arrives at a community ED at 2 AM after a minor automobile accident, complaining only of chest pain. His ECG is consistent with an acute MI. Thrombolytics are administered and the patient becomes terminal within minutes.

This patient experienced a massive hemothorax. A thorough exam would have revealed chest wall contusions from the steering wheel, consistent with BCI and thoracic aortic injuries. Recent head injury and severe trauma are contraindications to thrombolytics. Remote incidents or mild musculoskeletal trauma are relative contraindications.

Case 2

A 19-year-old woman is admitted to a university hospital for a low-grade splenic laceration and severe cervical strain sustained upon being struck by a vehicle. Though hypotensive in the ED, the patient has an uneventful in-patient course and is discharged 3 days later in a Miami J collar with the following vital signs: blood pressure (BP) 100/72, heart rate (HR) 114, respiratory rate (RR) 16, and oxygen saturation (O_2 Sat) 98%. Twenty-four hours later, she presents to the ED complaining of severe mid-epigastric pain. Vital signs are BP 80/40, HR 130, RR 20, O_2 Sat 96%, and Temp 98.3. One hour later an abdominal CT is normal and the patient's vital signs remain unchanged despite 2 liters of fluid and a stable hematocrit. A subsequent bedside FAST reveals a pericardial effusion.

This patient presents with delayed hemopericardium and tamponade from a small tear in the right atrium. Initially, hypotension in the setting of a minor splenic laceration should have alerted the clinicians to a missed injury. An unexplained abnormal ECG (tachycardia) on discharge warrants an echocardiogram in this setting. Jugular vein distention, a classic finding, may be a late or nonexistent finding in the BCI patient with multi-organ or multi-extremity injuries. Beware of the concealing cervical collar.

Case 3

A 55-year-old trauma patient with multiple extremity fractures is to be discharged at change of shift. The patient had required intubation for agitation and had received 5 liters of fluid for hypotension. On reassessment, you notice that the patient's O_2 Sat is 95% on 100% fraction of inspired oxygen (FiO_2) and there are diffuse rales. An X-ray is obtained, and the radiologist confirms that the patient has pulmonary edema. Furosemide is administered. The patient becomes hypotensive and arrests.

Pulmonary edema is a common presentation in patients with papillary muscle rupture, aortic rupture, and ventricular contusion. Valvular incompetence should be evaluated emergently by a cardiothoracic surgeon for repair. Treatment for ventricular failure includes fluids, pressors and inotropes, preferably guided by the use of a pulmonary artery catheter. Consider an intra-aortic balloon pump for refractory cardiogenic failure.

Case 4

A patient presenting from a 30-foot fall loses his vital signs upon arrival at the ER. Emergent thoracotomy and pericardiotomy is indicated when the patient develops rapid cardiovascular decline and cardiac arrest in the ED.

A pericardiocentesis is performed blindly. Blood is aspirated; it clots immediately. The exam is declared negative; there is no hemopericardium. Thirty minutes later the patient arrests. Thoracotomy reveals a large pericardial effusion.

Blind, inadvertent aspiration from the intracardiac chamber may lead to a false negative diagnosis. Lacerated cardiac vessels or ruptured chambers can bleed quickly into the pericardial sac and will clot. Sonographic or electrocardiographic guidance may assist in averting technical miscalculations.

Case 5

A 14-year-old boy presents after losing consciousness at home while shadow boxing with his 6-year-old brother. He only complains that his chest "feels weird." This patient's presentation is consistent with commotio cordis. Electrocardiographic changes including ventricular fibrillation, heart block, and ST changes have been described. The patient should receive an ECG and appropriate electrical cardioversion or antiarrhythmic therapy, if indicated.

Blunt Cardiac Injury with Coronary Artery Thrombosis

Coronary artery lesions represent less than 2% of BCIs. Direct precordial impact, crushing between sternum and spine, and resultant myocardial edema are the proposed causative mechanisms. Coronary artery contusion, spasm, disruption of coronary plaque, laceration, dissection, and occlusion have all been described in the literature. Anginal-type chest pain, myocardial ischemia and infarction are common outcomes. The left anterior descending is more commonly injured than the right coronary artery (69, 70).

The ECG often demonstrates ST segment elevation or changes consistent with an infarction or ischemia (71). Such findings warrant an emergent echocardiogram and/or angiography. Prompt consultation with a cardiologist and/or cardiothoracic surgeon is also essential. Management options should not differ from those of the typical myocardial infarction patient. Conservative therapy, percutaneous coronary angioplasty, and thrombolytics are appropriate interventions. The option instituted should be weighed against concomitant injuries, hemodynamic status, and possible contraindications to anticoagulation or thrombolytic use (71). On long-term follow-up, sequelae range from complete recovery to cardiac complications of angina, congestive heart failure, and death (72).

Conclusion

Since there are no standard diagnostic criteria for BCI, the true incidence of blunt cardiac injury remains unknown. Signs and symptoms suspicious for cardiac injury warrant expeditious workup to exclude lethal injuries. ECG remains a sensitive test for BCI; however, all changes and dysrhythmias must be presumed to be suspicious in order to avoid missed injuries. The addition of troponin I is an option that may serve to identify those patients at increased risk of mortality, especially if the ECG is abnormal. Although it appears that troponin I is more predictive than CK-MB of an adverse outcome, the physiologic nature and timing of troponin release remains unclear. The utility of troponin I in predicting long-term BCI morbidity is also undetermined. Patients with ECG abnormality and troponin elevation or arrhythmias are clear candidates for telemetry monitoring. Echocardiography should be reserved for patients who have a complicated inpatient course or undifferentiated clinical scenarios that warrant investigation, i.e., persistent chest pain or shortness of breath. If the patient exhibits signs of hemodynamic instability, an echocardiogram is indicated to identify life-threatening injuries. Placement of a pulmonary catheter may further assist in the hemodynamic management of the unstable patient. The infrequent coronary artery thrombosis should be managed expeditiously and its management weighed against that of other injuries and co-morbidities. Future studies identifying the independent risk factors of critically ill BCI patients remain needed.

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Patient Noncompliance:

Causes and Solutions

Fred Rosner, M.D., M.A.C.P.

Abstract

This essay examines the subject of patient noncompliance with prescribed medications or other health regimens and its possible causes, and discusses possible solutions. Noncompliance or nonadherence to prescribed medical regimens may have serious detrimental effects on the patient's health and quality of life, and may lead to further morbidity or mortality. Proposed solutions to the problem of noncompliance are many (Table 3). If aggressively pursued, they may help improve the health of individual patients and the general community.

Key Words: Compliance, noncompliance, adherence, nonadherence.

Introduction

Poor compliance (or adherence) by patients with prescribed medication or other caregiver recommendations such as lifestyle changes is a widely acknowledged problem. There is inconsistent and inconclusive evidence for the effectiveness of various approaches to improve compliance (1). A recent study of multi-compartment medication devices, for example, showed limited success in promoting adherence among nonadherent adults living at home (1).

This essay examines the subject of patient noncompliance and its possible causes, and discusses possible solutions to ameliorate the problem and increase patient adherence to prescribed medications or other health regimens. Poor compliance is an important health care problem, which can result in reduced efficacy or failure of the recommended intervention, with detrimental effects on the patient's health, on the effective use of limited health care resources, and on evaluating the "real" clinical efficacy of health care interventions (2).

Literature Review

In one study of patients with chronic pain, the authors showed that, although patients reported high compliance with maintaining paper diaries, actual compliance was low and hoarding was common (3). The excellent compliance achieved with electronic diaries indicates that low compliance was not due to the particular sample of patients or an overly burdensome protocol. These results call into question, conclude the authors, the validity of paper diary records.

In a review of compliance with pelvic floor exercises by women with stress incontinence (2), the author reviews the literature on compliance and the factors that might influence it. The author concludes that motivation is a critical prerequisite for influencing compliance with the intervention and it ultimate success. Factors to optimize motivation are suggested.

Kesteloot points out that "noncompliance" usually refers to patients' failure to follow health interventions as recommended by the health care provider, but it can also refer to the providers' failure to act according to practice guidelines or standards of care (4). The author discusses the economic implications of noncompliance in health care, concluding that it is not enough to investigate the effectiveness of interventions that enhance compliance. The intervention's benefit in terms of increasing patients' quality of life must be weighed against the costs of the interventions. Such a bal-

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ance will help to "guarantee efficient allocation of scarce resources in health care" (4).

Kane et al. studied the effects of nonadherence to medication among patients with quiescent ulcerative colitis (5). They conclude that nonadherence is associated with clinical recurrence of disease and recommend that researchers (a) determine why patients are nonadherent and (b) develop disease-specific interventions to improve adherence or compliance.

Voss et al. studied the effects on compliance and quality of life among postmenopausal women taking hormone replacement therapy (6). They point out that ensuring long-term compliance is one of the major challenges in the prevention and early treatment of postmenopausal osteoporosis. Among other things, they conclude from their study that less anxiety about the medication was associated with higher treatment satisfaction and better compliance with the regimen. Similarly, Thomas et al. found that HIV patients who discontinued their drug therapy did so because they felt that their body "needed a break from the drugs" or because the drugs made them not feel good or they wished to try a more holistic approach (7).

Pumilia describes a case study of compliance related to the psychological impact of the physician-patient relationship (8). Studies seeking to identify the typical "profile" of a noncompliant patient have been mostly unsuccessful. The author concludes that there are a myriad of factors underlying a patient's noncompliance as well as mechanisms through which attempts can be made to address it. Resolving noncompliance, unfortunately, is often a task that requires more time and energy than is available to the physician. Physicians and medical teams and psychologists provide the most effective and efficient foundation for addressing not only patient noncompliance but also "the enhancement of factors that lead to enduring relations between physician and patient throughout the course of treatment" (8).

In a study of dietary and fluid compliance of Chinese hemodialysis patients, Lee and Molassiotis found that more than half of the dialysis patients did not comply with fluid restrictions (9). Compliance varied according to the patients' dietary knowledge and health beliefs. They recommend patient education and family involvement to improve compliance.

Discussing methods to improve elderly patient compliance with taking medication, Banning suggests that patients be given the least complex combination of drugs (10).

Patients should also be given printed forms of information to supplement the oral teaching of the treatment regimen by the physician or nurse. Joel Hill reminds us that for many physicians the noncompliant patient compromises the ideal of medicine as a healing art, since their patients' functional ability and quality of life depend on their success at self-care (11). Metcalf-Wilson proposes a model of three C's (confidentiality, communication and compliance) to help create an environment that will provide competent, holistic, quality care to adolescent patients (2). DiMatteo examines emerging issues in consumer-provider communication and patient adherence to cancer screening and prevention, diagnosis, treatment and coping with the loss of a loved one. She reports that many factors affect adherence and that these can be supported or hindered by provider-patient relationship, patient's beliefs, social and cultural norms, family and social support, mood and behavioral management (13). Worth and Dhein conclude that patient education may modify the behavior of patients in the management of COPD by improving their self-control and self-management of the disease and thus reducing mortality (14). Gray et al. review the literature on compliance as well as interventions to enhance compliance with antipsychotic medications (15). They point out that noncompliance with antipsychotic medication is observed among approximately 50% of patients with schizophrenia and offer possible solutions to achieve compliance (see Table 3).

Murray et al., in a randomized controlled trial of training patients in self-management of warfarin treatment, concluded that such training is feasible, practical and cost-effective (16). Sewitch et al. studied medication nonadherence among women with fibromyalgia (17). The authors conclude that "unintentional non-adherence was predicted by community subjects not being under a rheumatologist's care, less disease activity, less use of instrumental coping ['task-oriented strategies to deal with the illness'] and higher patient-physician discordance. Intentional nonadherence was predicted by shorter duration under a rheumatologist's care and higher patient-physician discordance." The authors also conclude that "the therapeutic relationship, in addition to [its] clinical and psychosocial characteristics, influenced nonadherence to medication" (17).

Cotter and his colleagues studied the lack of aspirin effect and examined two possible reasons: aspirin resistance or resistance to taking aspirin (18). The authors concluded that nonadherence is a significant mediator of poor outcome in myocardial infarction and that it is important to evaluate whether or not patients are taking their medications. Hartigan points out that patient education is vital to promote patient safety, optimal dosing and adherence to the treatment plan (19). Calsyn et al. report that noncompliant patients in a modified opioid substitution program can benefit and improve compliance without an associated significant increase in harm in the larger clinic population (20). Nearly three quarters of the patients placed in a minimal services track were retained in treatment and more than one third of them improved sufficiently to return to the regular opioid substitution program. The minimal services track was the basis of improved compliance. Gethin outlines the concept of patient compliance and its relevance to the care of patients with chronic wounds (21).

In order to improve compliance with prescribed regimens, the patient must be involved in the decision-making process and fully supported by professionals. This requires the multidisciplinary team to allow enough time to educate patients, listen to fears and anxieties and deal with them as much as possible, and provide the support that patients need. Uribe et al. describe factors predictive of poor compliance with study visits in three ethnic groups of patients with systemic lupus erythematosus (22). Noncompliant patients were more likely to be young, unmarried, of African American ethnicity, live closer to the medical centers, and have longer disease duration and greater disease activity as assessed by the physician. The authors will use the information they have gathered to develop interventions to reduce noncompliance.

Kennedy and Erb "showed that about 1.3 million adults with disabilities did not take their medications as prescribed because of cost and [that] more than half reported health problems as a result" (23). The authors conclude that "prescription noncompliance due to cost is a serious problem for many adults with chronic disease or disability."

David Bartels discusses adherence to oral therapy for type 2 diabetes (24). The author points out that studies have demonstrated that treatments including multiple medications or frequent dosing have a negative impact on adherence. Several approaches have been used to improve adherence, including increased communication between health care providers and patients, implementation of multidisciplinary programs and the use of easier dosing regimens (i.e., reduced number of drugs or doses per day). Morris addresses the issue of dosing frequency in diabetes and suggests a simple approach to improving adherence to therapy and clinical outcomes, (i.e., the use of "diabetes drugs that simplify or reduce the number of daily doses required") (25). The author points out that treatment adherence is a major issue in the effective management of any chronic illness. For diabetes, treatment adherence is the key to maintaining tight glycemic control, which in turn reduces the risk of long-term complications.

A number of factors that contribute to nonadherence in chronic illness have been identified. These must be addressed to improve adherence and better health outcomes for patients. Patel et al. report on the acceptability of and compliance with hip protectors among community-dwelling women at high risk of hip fracture (26). The authors conclude "that only a minority of [these] women will wear hip protectors to reduce fracture risk."

Singleton et al. provide a historical perspective on the term "compliance," postulating that such a perspective provides a framework for discussion of approaches to compliance identified from the research literature (27). The authors draw an analogy between these approaches and leadership styles, which raises the question of the role provider style plays in patient compliance.

Pinikahana et al. explore the complexity of compliance in schizophrenia (28). They review socio-demographic characteristics of these patients, including age, gender and socioeconomic status; illness factors such as insight, symptoms, duration of illness, substance abuse, adverse effects of medication; psychosocial factors such as health beliefs and social support; and treatment factors including the patient-physician relationship. The authors conclude that these factors provide important information to guide the caregiver (physician and mental health nurse) in facilitating patient compliance (28).

Banning considers medication management among older people and explains how nurses can work with patients and other professionals to improve concordance (29).

Discussion

The literature on noncompliance is so vast that I singled out several categories on noncompliance for additional consideration: nonadherence in cardiology, in pediatrics, among older patients and among HIV/AIDS patients.

Nonadherence in Cardiology

We have already discussed above a study of adherence to taking aspirin among patients at risk of developing myocardial infarction (18) as well as a study of compliance with warfarin therapy (16). A conceptual map for studying long-term exercise adherence in a cardiac population is provided by Graham (30). Diehl strongly suggests the need for more vigilant hypertension treatment (31). The author offers strategies for improving adherence to therapy, including patient education, family support, individualized therapy for each patient's needs and situation, self-monitoring of blood pressure, telephone follow-up, and the use of combination therapy, which has fewer side effects and, in some cases, costs less (31).

Noncompliance among Elderly Patients

Evangelista et al. discuss compliance behaviors of elderly patients with advanced heart failure (32). They studied six prescribed activities by elderly (≥ 65 years) and younger (<65) patients: medical appointments, medication, diet, exercise, smoking cessation and alcohol abstinence. Elderly patients were more compliant with diet and exercise than their younger counterparts. There was no difference in the other health care behaviors.

Half the elderly patients reported some degree of difficulty complying with exercise, while 37%, 24% and 23% had difficulty following the diet, keeping follow-up appointments and taking medications, respectively. Only 9% of elders continued to smoke and 18% continued to drink alcohol.

The authors conclude that strategies to help older patients minimize perceived difficulties associated with health care regimens may improve compliance and long-term morbidity and mortality from heart failure. Neily et al. studied potential contributing factors to noncompliance with dietary sodium restriction among patients with heart failure (33). The authors concluded that on referral to a specialty heart failure clinic, many patients have severe deficiencies in their knowledge base regarding dietary sodium intake that would preclude compliance with the sodium restriction guidelines. Directed education focusing on sodium intake corrected many of these deficiencies (33).

Sherry and co-workers discuss a case of noncompliance in heart transplantation that ultimately resulted in the death of the patient (34). They point out that noncompliance with the prescribed medical treatment regimen has been implicated as a major risk factor for morbidity and mortality after heart transplantation. Szekendi reports that compliance with acute MI guidelines lowers inpatient mortality (35). Daly et al. review the barriers to participation in and adherence to cardiac rehabilitation programs (36). They point out that only one third of patients maintain attendance in these programs after six months and they discuss factors associated with nonadherence, such as being older, female gender, fewer years of formal education and others.

Sebate and DeGeest state that poor adherence is the primary reason for suboptimal benefit for patients with chronic diseases (37). They call for nursing managers and policymakers to play an active role in addressing the major problem of patient nonadherence to the prescribed treatment regimen.

Nonadherence in Pediatrics

Watson and Forshaw point out that child outpatient nonattendance may indicate welfare concerns (38). Lamberth et al. compared the rates of missed appointments among pediatric patients in a private practice for patients receiving Medicaid and those with private insurance (39). The authors discuss why many pediatricians do not accept Medicaid patients. They quote a study that showed that the rate of missed appointments was three times higher among patients with Medicaid than among patients with private insurance.

McPherson et al. discuss noncompliance with medical follow-up after pediatric intensive care (40). In a cohort of 111 critically ill children, the authors found that lack of ordered medical follow-up did not affect emergency visits. However, 28% of the patients did not receive timely medical follow-up. No socioeconomic or demographic risk factors were identified for noncompliant patients. However, severity of illness, longer PICU stay and longer hospital stay as well as the number of follow-up appointments ordered were predictors of noncompliance. The authors conclude that the potential exists for implementing strategies to improve compliance in identified populations (40).

Toole and Berry discuss the subject of increasing immunization compliance among children (41). School-based immunization reflects a growing trend in the area of health care, because children spend at least 25% of their day in school. The authors point out the challenges in successfully implementing a school immunization program, including the availability of working parents, lack of access to primary care, lack of transportation, and the impact of the Health Insurance Portability and Accountability Act (HIPAA).

The authors describe an immunization project that removed almost all of those barriers for high-risk students and gave the school nurses tools to succeed in achieving higher levels of immunization compliance in inner-city schools. Since the project's inception, compliance in the district has risen from an overall level of 50–60% to 90–100%, along with better record keeping and the prevention of exclusions from school (41). The removal of the barriers to compliance was the reason that this project was so successful.

Noncompliance with HIV/AIDS Therapy

Murphy et al. discuss the barriers to highly active antiretroviral therapy (HAART) among HIV-infected adolescents (42). They conclude that adherence was tied closely to daily routine, which supports the assumption that helping adolescents improve their organizational skills may be necessary to improve adherence. Patient-level intervention, provider-level intervention, and health care system modification may all be necessary to improve HIV-infected adolescents' adherence to HAART (42). Tucker et al. point out that medication regimens for HIV infection are complex and inconvenient, often produce side effects, and must be taken consistently for long periods of time in order to improve prognosis in HIV disease (43). More important, perhaps, their findings suggest a correlation between nonadherence and the presence of emotional disorders and/or substance abuse problems, and thus "the need for screening and treatment for mental health and substance use problems among HIV-positive patients to improve adherence to antiretroviral medications" (43).

Painter and his colleagues performed a qualitative interview study to assess women's reasons for not participating in follow-up visits before starting short-course antiretroviral prophylaxis for prevention of mother-to-child transmission of HIV (44). The authors concluded that difficulties experienced by women during their contacts with staff working on a prevention program and negative views that the women have about the program can contribute to their nonparticipation in prophylaxis. Training and supervision of program staff may increase the likelihood of positive interactions between staff and clients, thereby facilitating women's participation in preventing transmission of HIV from mother to child. Outreach and mobilization in communities that are served by prevention programs may complement these measures by contributing to increased social support for women's efforts to prevent HIV transmission (44).

Allardice provides a clinical update on HAART medication adherence in the era of highly active antiretroviral therapy (45). She concludes that health care providers need to genuinely consider a holistic approach to care. Strategies need to be developed to accurately assess a client's readiness to begin therapy, and support that acknowledges a client's experiences needs to be put in place. Health care providers need to change the model to make it fit the client rather than asking the client to adapt to an inflexible model that doesn't allow for life getting in the way (45).

Ramirez Garcia and Cote discuss the factors affecting adherence to antiretroviral therapy among patients living with HIV/AIDS (46). They point out that "antiretroviral treatments have given hope to people living with HIV/AIDS and play a role in improving their quality of life. However, the effectiveness of these treatments is directly related to the level of adherence and commitment to them. Researchers have [shown] many factors that play an important role in adopting and maintaining adherence behavior. ...the authors present an in-depth review of the literature and...enumerate the factors that link adherence behavior to the individual, the treatment, the illness, and the relationship with the health professional. An understanding of these factors," conclude the authors, "is essential to develop interventions that will improve adherence to therapeutic regimens among people with HIV/AIDS" (46).

Both Benarroch and Ammassari describe the effects of cognitive dysfunction and treatment regimen complexity on medication adherence among HIV-positive adults (47, 48).

Summary and Conclusions

Nonadherence or noncompliance with prescribed medical regimens for a variety of disorders and diseases is a serious problem in pediatric, adult and elderly population groups, both among males and females and among people of all ethnic, cultural and religious backgrounds. Such poor compliance or noncompliance may have seriously detrimental effects on the patient's health and quality of life, and may lead to additional morbidity and mortality.

Noncompliance or nonadherence to prescribed medical regimens may also lead to additional diagnostic testing, added discomfort to the patient, increased cost to both the patient and the health care system, and a deterioration or increased discordance in the doctor-patient relationship.

Factors that are associated with nonadherence (Table 1) can be classified as patient factors, treatment factors and lifestyle factors (21) as well as demographic factors, psychosocial factors and sociodemographic factors (34). Possible adverse effects from a patient's noncompliance with the treatment regimen are summarized in Table 2.

Various solutions to the problem of noncompliance have been proposed. These are detailed in Table 3.

There is no clear evidence that the application of the enumerated suggestions in Table 3 will lead to the desired outcomes. However, the serious problem of patient nonadherence to prescribed medical regimens can be addressed aggressively and possibly overcome in many situations by using one or more of these suggestions. If successful for some patients,

TABLE 1
Possible Causes of Patient Noncompliance

A. Patient Factors
1. Lack of knowledge about the treatment regimen.
2. Lack of motivation and/or inconvenience.
3. Lack of self-esteem.
4. Beliefs and attitudes concerning the effectiveness of the treatment regimen—cultural and ethnic patient background.
5. Lack of a positive patient-physician relationship.

B. Treatment Factors
1. Impact on the patient's lifestyle and need for changes.
2. Complexity of the treatment and extended duration.
3. Patient's ability to comply with treatment regimen.
4. Comfort or discomfort associated with treatment regimen.
5. Physician-patient discordance.

C. Lifestyle Factors
1. Environmental limitations such as poor housing.
2. Resource limitations such as no transportation to the clinic.
3. Occupational limitations such as the patient's need to return to work or resume household duties.
4. Lack of awareness of illness and consequences of noncompliance.

D. Sociodemographic Factors
1. Age, educational level, smoking, drinking, illegal drug use.
2. Marital and socioeconomic status, lack of social support system.

E. Psychosocial Factors
1. Lack of self-motivation, depression, anxiety.
2. Patient's perceptions, beliefs and attitudes.
3. Lack of interest, lack of time or inconvenience, cost to patient and complexity of treatment regimen (high dosing frequency).
4. Worries about side effects of the treatment, fear.
5. Dependency on others or denial of illness.
6. Previous poor experience with a treatment regimen.
7. Fear of weight gain, forgetfulness, indifference.
8. Feeling of doubt, vulnerability and side effects.

Modified from references 21 and 34.

TABLE 2
Possible Adverse Outcomes Related to Noncompliance with Medication Regimens

1. Worsening or aggravation of the illness.
2. Decreased quality of life.
3. Additional diagnostic testing.
4. Added discomfort to the patient.
5. Increased costs to the patient and health care system.
6. Deterioration of physician-patient relationship.
7. Adverse effects on the patient's health.

TABLE 3
Proposed Possible Solutions to the Problem of Patient Noncompliance with Treatment Regimen

1. Provide patients with multi-compartment medication devices to help them with the complexity of the regimen.
2. Provide patients with paper or electronic diaries to record their daily medication use.
3. Provide patient with better education.
4. Improve the patient-caregiver relationship.
5. Offer patients monetary or other rewards for compliance.
6. Attempt behavior modification techniques.
7. Provide educational and cognitive strategies.
8. Motivate patients to comply—give reasons for the need to comply.
9. Establish phone and letter contacts with patients.
10. Establish an environment of trust between the caregiver and the patient.
11. Provide an atmosphere of cooperation and mutual involvement.
12. Provide effective communication between patient and caregiver.
13. Assist the patient with needed lifestyle changes such as smoking cessation.
14. Involve the family of the patient to promote compliance
15. Remove barriers to compliance, if possible
16. Reduce the complexity of the medication regimens
17. Preferentially prescribe longer-acting medications.
18. Use medication teaching programs, but be sure to give information that is easily understood and assimilated by the patient over a period of time.
19. Repeat the education if necessary. The education should be patient centered and specific for each medication.
20. Improve provider-patient relationship by taking into account the patient's beliefs, social and cultural norms, family and social support.
21. Try mood and behavioral management, if available.
22. Provide education to modify the behavior of the noncompliant patient by improving self-control and self-management of the illness or disorder, thus reducing morbidity and mortality and increasing compliance.
23. Although education increases the patient's understanding of the illness, it does not necessarily improve compliance. Interventions such as compliance therapy based on cognitive behavioral techniques appear to be effective in enhancing compliance of psychiatric patients (15).
24. Education needs to be tailored for each individual patient using resources such as medication information sheets to reinforce the teaching.
25. Encourage family support and use of telephone follow-up.
26. Individualize therapy for the patient's unique needs and situation.

these techniques can then be tested on a wider scale with other noncompliant patients. The possible benefits clearly make the effort worthwhile.

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The Effects of the Prophylactic Tropisetron-Propofol Combination on Postoperative Nausea and Vomiting in Patients Undergoing Thyroidectomy under Desflurane Anesthesia

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Abstract

Purpose: To evaluate the efficacies of tropisetron and tropisetron-propofol combination in the prophylaxis for postoperative nausea and vomiting in patients undergoing thyroidectomy under desflurane anesthesia. (This combination has apparently not been previously investigated for this particular surgery and anesthesia.)

Methods: Prospective, randomized, double-blind study. One hundred five patients aged between 19 and 68 years were included in the study. Group T received 5 mg of tropisetron (tropisetron group, n=35), group TP (tropisetron-propofol group, n=35) received 5 mg of tropisetron and 0.5 mg/kg of propofol, and group P (placebo group, n=35) received saline, immediately after anesthesia induction. The anesthesia induction regimen was applied to all patients, and anesthesia was maintained with 5–7% desflurane and 66% N_2O in O_2.

Results: Group TP reported a lower incidence of postoperative nausea and vomiting (17%) than those in groups T and P (42.8% and 77%, respectively). The postoperative antiemetic requirements were significantly higher in the placebo group compared to the other two groups ($p<0.05$).

Conclusion: The tropisetron-propofol combination is more effective than tropisetron alone in the prevention of postoperative nausea and vomiting after thyroidectomy.

Key Words: Side effects, postoperative, nausea, vomiting, antiemetic, tropisetron, propofol, surgery, thyroidectomy, anesthetics, desflurane.

Introduction

STUDIES REPORT that the frequency of postoperative nausea and vomiting (PONV) after thyroidectomy is approximately 63–84%, for anesthetic agents other than desflurane (1, 2). PONV may represent the principal source of discomfort of the entire procedure, and the most unpleasant aspect of postoperative recovery. Additionally, vomiting may increase the risk of postoperative bleeding (3). Also, increased thoracic and abdominal pressure during retching may produce arterial and venous hypertension. Postoperative bleeding is of particular concern in these patients, as it may produce hematoma in the neck with the potential for airway obstruction.

Desflurane has a low blood/gas solubility that allows rapid induction and recovery. This characteristic has recently made it increasingly popular. However, PONV, the most significant side effect, is frequent (4).

Tropisetron, a highly potent and selective antagonist of serotonin type 3 receptors (5-HT_3), has proven to be effective and well tolerated against nausea and vomiting induced by radiotherapy and chemotherapy (5). It is also effective and well tolerated in the prevention or treatment of PONV in women undergoing gynecologic surgery and laparoscopic cholecystectomy (6, 7).

The numerous studies on the antiemetic effect of propofol at subhypnotic doses have yielded controversial results. Campbell et al. (8) reported that propofol at subhypnotic doses was ineffective against PONV after laparoscopic cholecystectomy, whereas Fujii et al. (9) achieved adequate prophy-

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laxis in patients undergoing thyroidectomy under sevoflurane anesthesia. However, propofol at subhypnotic doses was reportedly ineffective after procedures under desflurane anesthesia (10).

Therefore we investigated the efficacies of the tropisetron and tropisetron-propofol combination in PONV prophylaxis, in patients undergoing thyroidectomy under desflurane anesthesia. (This combination has apparently not been previously investigated for this particular surgery and anesthesia.)

Materials and Methods

After the study protocol was approved by the ethics committee of the University Hospital, 105 patients between 19 and 68 years of age were enrolled. Patients who had gastrointestinal problems, had used a central-acting drug or an antiemetic in the previous 24 hours, were having menstruation or had a history of nausea and vomiting were excluded. The patients were randomized to 3 groups. Group T received 5 mg of tropisetron (n=35), group TP (n=35) received 5 mg of tropisetron and 0.5 mg/kg of propofol, and group P (n=35) received saline, immediately after anesthesia induction. The same anesthesia regimen was administered to all patients. After the patients had been taken to the surgery room, mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SpO_2) were monitored. Patients were assigned to one of the three study groups using a computer-generated random number table. Induction was performed with fentanyl (1 μg/kg) and thiopental (6 – 7 mg/kg); vecuronium (0.1 mg/kg IV) was given to facilitate tracheal intubation. Maintenance was conducted with 5 – 7% desflurane and 66% N_2O in oxygen. The patients were ventilated to maintain the end-tidal CO_2 level between 30 and 35 mm Hg (Datex Engstrom AS/3 Anesthesia monitor, Helsinki, Finland). Muscle relaxation was maintained with IV vecuronium. The thyroidectomy was performed with patients in the supine position, with the head slightly hyperextended. At the end of the operation, atropine (0.02 mg/kg IV) and neostigmine (0.05 mg/kg) were used to reverse the neuromuscular block. The extubation time (the interval between the cessation of anesthetic gas and extubation), emergency time (the interval between the cessation of anesthetic gas and eye opening) and orientation time (the interval between the cessation of anesthetic gas and the time when the patients could state the current date and their birth date) were recorded.

Postoperatively, the patients were taken to the recovery room. Pain was assessed by means of a visual analog scale (VAS 0: no pain; 10: the most severe pain). Patients with VAS scores higher than 3 were given 75 mg of diclofenac intramuscularly. We evaluated nausea and vomiting by direct questioning or by spontaneous complaint of patients and recorded for the 0 – 2, 2 – 6, 6 – 12 and 12 – 24 hour intervals. The nurses asked the patients if retching or vomiting had occurred and if they felt nauseated, with only two possible answers (yes or no). Nausea was defined as the unpleasant sensation associated with awareness of urge to vomit; retching was defined as labored, spasmodic, rhythmic contraction of the respiratory muscles without expulsion of gastric contents, and vomiting was defined as the forceful expulsion of the gastric contents from the mouth. No distinction was made between vomiting and retching (i.e., a retching event was considered as a vomiting event). A complete response was defined as no PONV and no need for rescue antiemetic medication. Patients with two or more episodes of vomiting were given metoclopramide (10 mg) intravenously. The intraoperative and postoperative complications were recorded.

Categorical variables were analyzed by using a series of 3×2 Chi-squared tests to determine the differences among the three groups, followed by 2×2 Chi-squared test for intergroup differences. All follow-up analyses were corrected for the number of simultaneous contrasts using the Bonferroni adjustments. A p value <0.05 was considered statistically significant.

Results

The groups did not differ significantly with respect to demographic characteristics, operation and anesthesia durations ($p>0.05$) and there were no significant differences in their extubation, emergency and orientation times ($p>0.05$) (Table 1). The patients' number of PONV and rescue antiemetic requirements are presented in Table 2. Group TP reported a lower incidence of postoperative nausea and vomiting (17%) than those in Group T and Group P (42.8% and 77%, respectively). The postoperative antiemetic requirements were significantly higher in the placebo group compared to the other two groups ($p<0.05$)

Discussion

In this study of thyroidectomy under desflurane anesthesia, the tropisetron-propofol combination was more effective than tropisetron alone or placebo in antiemetic prophylaxis.

The etiology of PONV after thyroidectomy is unclear, but it does occur frequently. This high inci-

TABLE 1

Demographic Data and Anesthesia Duration, Surgery Duration, Extubation, Emergency, and Orientation Time of the Research Groups

	Group T (n=35)	Group TP (n=35)	Group P (n=35)
Age (years)	42.0 ± 11.6	46.2 ± 13.5	43.1 ± 11
Height (cm)	163.3 ± 8.3	162.5 ± 5.7	164.3 ± 9.1
Weight (kg)	70.9 ± 11.9	66.8 ± 9.1	72.0 ± 13.5
Sex M/F	7/28	5/30	6/29
Anesthesia duration (min)	122.0 ± 38.5	116.0 ± 34.7	120.5 ± 33.9
Surgery duration (min)	111.8 ± 37.7	105.2 ± 32.8	109.0 ± 31.0
Extubation time (min)	2.4 ± 1.0	2.6 ± 1.4	2.8 ± 2.0
Emergency time (min)	4.3 ± 1.4	4.7 ± 2.5	4.5 ± 2.5
Orientation time (min)	6.8 ± 1.8	6.9 ± 2.6	6.4 ± 3.0

Values are mean ± SD.

TABLE 2

Number of PONV and Rescue Antiemetic Requirements for the Research Groups

	Group T (n=35)	Group TP (n=35)	Group P (n=35)
Complete response (no PONV, no rescue)	20 (57.2)*	29 (83)*+	8 (23)
Nausea	15 (42.8)*	6 (17)*+	27 (77)
Retching or vomiting	8 (22.8)*	2 (5.7)*	25 (71.4)
Total	15 (42.8)*	6 (17)*+	27 (77)
Rescue antiemetics	8 (22.8)*	2 (5.7)*	25 (71.4)

Values are number of patients n (%)
* p value (χ^2 test) for comparison with placebo group, + p value (χ^2 test) for comparison with tropisetron group
PONV: Postoperative nausea and vomiting

dence is probably related to the age range and sex of the patients (mostly middle-aged woman) and the intense preoperative vagal stimulation (surgical handling of the neck structures) (1). Obesity, anesthesia technique and postoperative pain are also known to increase the frequency of PONV (11). We tried to minimize the effects of these factors by standardizing patient characteristics, surgical procedure, anesthesia technique and postoperative pain control.

The frequency of PONV after desflurane anesthesia is reportedly higher than the frequencies after sevoflurane and isoflurane anesthesia, but rapid recovery is an important advantage (12). Gupta et al. (12), in a meta-analysis of 58 articles published between 1966 and 2002, concluded that desflurane allows rapid recovery, but the frequency of PONV is high. Raeder et al. (13) reported that in laparoscopic cholecystectomy, desflurane cost less and allowed rapid recovery in comparison with propofol, but that prophylaxis for PONV was required. Van Hemelijck et al. (14) reported that use of propofol during induction in desflurane anesthesia was ineffective in preventing PONV. Therefore, we chose to investigate the effects of tropisetron and tropisetron-propofol combination.

Tropisetron is a potent selective 5-HT$_3$ receptor antagonist that has been successfully used to treat nausea and vomiting after chemotherapy and radiotherapy (15). Its efficacy against PONV has been confirmed (6, 16). Its elimination half-life (8 – 12 hours) is longer than that of the other 5-HT$_3$ antagonists (e.g., ondansetron 3.2 – 3.7 h, granisetron 3 – 4 h), and a single dose of tropisetron may provide prolonged antiemetic effects (16). In a series of 1513 patients undergoing general anesthesia, Alon et al. (17) found that tropisetron reduced the frequency of PONV and the rescue antiemetic requirement.

The mechanism by which propofol acts as an antiemetic is unclear. Propofol is not thought to have vagolytic properties. Borgeat et al. (18) suggested that propofol may have failed as an antiemetic in patients who had undergone laparoscopic gynecological procedures because of uninhibited vagal stimulation. In our study on patients undergoing thyroidectomy, an operation that causes strong vagal stimuli, the frequency of PONV decreased to as low as 17% with the tropisetron-propofol combination. However, the location and nature of this stimulation in laparoscopy and thyroidectomy are not comparable; in thyroidectomy they do not involve irritation or distension of gastrointestinal structures that may convey chemoreception or nociception via other afferents than parasympathetic. A dopamine D$_2$ receptor antagonist effect of propofol has also been suggested, but not proved (19). Propofol has also been shown to possess weak 5-HT$_3$ properties, suggesting a possible effect on the chemoreceptor trigger zone, but not enough to fully explain the efficacy of the drug in emetic syndromes refractory to 5-HT$_3$ antagonist therapy (20, 21).

Ewalenko et al. (22), in a study of patients undergoing thyroidectomy under isoflurane anesthesia, reported that postoperative propofol infusion (0.1 mL/kg/h) reduced the frequency of PONV to 44% compared to 84% in the placebo group. In a study by Fujii et al. (9) 0.5 mg/kg of propofol was more effective than droperidol and metoclopramide after thyroid surgery under sevoflurane anesthesia. However, in a study comparing sevoflurane and desflurane in patients undergoing laparoscopic cholecystectomy, Song et al. (10) found that 0.5 mg/kg of propofol decreased the frequency of PONV after sevoflurane but not after desflurane. Eriksson et al. (4) used desflurane, desflurane-ondansetron and propofol-based anesthesia in patients undergoing gynecologic operations and found PONV frequencies of 80% in the single-agent desflurane group, 40% in the desflurane-ondansetron group and 20% in the propofol-based anesthesia group. In our study, addition of tropisetron to propofol was effective in reducing the PONV frequency further.

In conclusion, the tropisetron-propofol combination is more effective than tropisetron alone for the prevention of PONV after thyroidectomy.

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Essays in Public Health and Preventive Medicine

COMMUNITY MEDICINE has long been a proud tradition at the Mount Sinai Hospital and the Mount Sinai School of Medicine. To signal the strong commitment of Mount Sinai to community health, the Department of Community and Preventive Medicine was established in 1967 with the founding of the Medical School. The Department was designated in the School's charter as a "third faculty" co-equal in status with the basic science and clinical faculties.

Vigorous teaching in community and preventive medicine is also a strong tradition at Mount Sinai. Since the Medical School's inception, we have taught an introductory core course in epidemiology and preventive medicine in the first year. Additionally, we have always sponsored a clerkship in either the third or the fourth year. In the early days, the clerkship consisted of community medicine field experiences, usually in East Harlem. More recently it has been combined with family medicine. We are very proud of the fact that Mount Sinai graduates have gone on to become director of the Center for Disease Control and director of CDC's Epidemic Intelligence Service program, and to occupy prominent positions in health departments nationwide.

From time to time it is important to refurbish old traditions. In that spirit, the Department of Community and Preventive Medicine made the decision in the academic year 2004–2005 to introduce a new requirement for a public health essay in the first-year course in epidemiology and preventive medicine. Each student in the course was asked to write a short essay on a topic of interest in the field of public health and preventive medicine. Students were specifically instructed to first describe the problem and then to propose a remedy. Complaining without curing is never enough. Our students rose magnificently to the challenge. The range of topics considered was broad, the analytical skill impressive and the product superlative.

Choice is always difficult, but the faculty carefully reviewed the 120 essays that were submitted and chose the six that we considered to be the best. These six essays are presented here with the enthusiastic permission of their authors. We are delighted to give these outstanding students an opportunity to present their work in a peer-reviewed journal, in their first year of medical school. We congratulate them on their achievement.

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A Call to Pharms: The Need for Tighter FDA Regulation of the Neutraceutical Industry

Joe Dobrin, B.A.

Beverly Hames sought a natural remedy for her persistent backaches. She visited an acupuncturist, who gave her a list of Chinese herbal preparations, some of which contained aristolochic acid. Two years later her kidneys began to fail. She ultimately received a kidney transplant and must now take anti-rejection medication for the rest of her life. Only later did she learn that the sale of aristolochic acid has been banned in several European countries due to its carcinogenic properties and its association with kidney failure. The Food and Drug Administration (FDA) issued a consumer warning in 2001, but the product remains on the market in the U.S.

Unfortunately, Ms. Hames' experience, cited in the May 2004 edition of *Consumer Reports*, is not unique. Many people take herbal supplements (also known as "neutraceuticals") under the mistaken impression that they are safer than regulated pharmaceuticals because herbal remedies are "natural" and don't contain "chemicals." The herbal supplement industry exploits this ignorance by implying that substances derived from plants are safer than chemicals synthesized in a lab. In fact, however, the active ingredients in herbal supplements are chemicals.

Although most herbal supplements are benign, some of these chemicals induce dangerous reactions in the human body. Aristolochic acid is far from the only chemical in herbal supplements currently on the market that has been associated with serious morbidity. The sexual stimulant yohimbine has been associated with heart and lung disease. The muscle-enhancing steroid androstenedione (andro), made famous by the baseball slugger Mark McGwire, increases cancer risk and decreases HDL (good) cholesterol. And kava, commonly found in energy drinks, is associated with liver damage. Although the FDA has recently issued warnings about the use of all of these chemicals, none has been banned from the market.

Unlike prescription drugs regulated by the FDA, there are no standards of quality or purity for neutraceuticals. This is because they are considered food additives, and as such, they are not subject to the much stricter drug regulatory authority of the FDA. There have been periodic calls for reform from medical and consumer protection groups. Unfortunately, these actions have achieved only a modicum of legislative success.

The central piece of legislation regulating herbal supplements neutraceuticals is the 1994 Dietary Supplement Health and Education Act (DSHEA). Although this law aimed to reduce the number of unsafe herbal supplements on the market, in practice it has had very little effect. Standing the drug regulation paradigm on its head, this act requires the FDA to demonstrate that a supplement is *unsafe* before it can ban it from the market, rather than placing the burden of establishing safety and efficacy on the supplement makers. As a result, the FDA takes on only the most demonstrably dangerous products, and even then the process often takes years.

Inadequate regulatory authority is not the only problem. Enforcement is hamstrung for two major reasons. First, authority is split between the FDA, which is charged with maintaining the safety of neutraceuticals, and the Federal Trade Commission (FTC), which ostensibly prohibits manufacturers from making unsupported claims of efficacy when advertising their products. In practice, lack of communication between these agencies has allowed many manufacturers to imply their products are effective without rigorous scientific testing to back up their claims. Second, neither of these agencies is adequately staffed or funded to achieve its mission. For example, the FDA's supplement division has a budget of $10 million and employs 60 people to regulate a $20 billion-a-year industry (*Consumer Reports*, May 2004). By contrast, Congress recently appropriated $515 million to fund nearly 3000 employees of the FDA's Center for Drug Evaluation and Research (*Drug Industry Daily*, Sept. 26, 2005) to regulate the pharmaceutical industry, whose annual sales are only 12 times the amount of supplement sales. It is little wonder that only a few dozen actions have been brought against supplement makers over the last decade.

The FDA's 2005 *Dietary Supplement Labeling Guide*, promulgated in April of 2005, has largely been a disappointment to reformers. The *Guide* intends that health claims made by herbal manufacturers be subject to much stricter standards. In theory, a neutraceutical manufacturer that wants to claim its product cures cancer must get prior approval from the FDA, and the claim must be supported by a consensus of the scientific literature. However, there is a large loophole. The FDA allows manufacturers to make "qualified claims" that require neither FDA approval nor a scientific consensus. They must merely cite *any* scientific study that supports their claim, and add a disclaimer (perhaps in fine print) that there is no scientific consensus about this finding. It is not difficult to imagine manufacturers citing obscure studies, potentially even from industry-funded labs, to meet this requirement.

Lest the industry miss the message that nothing has changed, the new guidelines are voluntary. As the guide says, "This guidance represents the Food and Drug Administration's (FDA's) current thinking on the topic. It does not create or confer any rights for or on any person and does not operate to bind [the] FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations."

It is time to change the way the FDA regulates herbal supplements. We must acknowledge that herbal supplements are drugs and should be regulated as such. The risks of not doing so will only increase.

Regulatory reform would place the onus on neutraceutical manufacturers to establish the safety and efficacy of their products. Only after subjecting these products to rigorous clinical trials to substantiate their claims should these products be allowed on the market, and then only with clear labeling of appropriate dosing and contraindications. To maximize compliance, enforcement should be centralized in only one agency—the drug regulatory division of the FDA, with significantly higher staffing and funding levels than the supplements division. By placing regulatory authority under the aegis of a division with teeth, the prognosis for future Beverly Hameses should be much brighter.

Dying in an Age of Specialists

Ben Harris, B.A.

I'VE BEEN WORRYING about my personal safety lately. I live only a couple of blocks away from Mount Sinai, where the directory lists seven faculty members who are certified by the American Board of Obstetrics and Gynecology to practice gynecological oncology. You might think that my fears are unfounded. After all, I am a male and cancer-free (to the best of my knowledge) so odds are that none of these people will ever be in a position to compromise my personal safety, right? Right, but it's the statistics that have been worrying me.

In the United States, the American Medical Association estimates there is one gynecological oncologist per 700,000 people in the general population. The last time I checked, there weren't 4.9 million people living in Manhattan, let alone the Upper East Side. Also, rumor has it that there are more gynecological oncologists practicing two miles away at Sloan Kettering. This preponderance of gynecological oncologists worries me because, according to the latest research, living in a county or state with a high concentration of specialist physicians can be hazardous to your health.

In a recent report in *Health Affairs*, Barbara Starfield, a University Distinguished Professor at the Johns Hopkins School of Public Health, reports that even after controlling for such variables as income, education, employment, ethnicity and population density, Americans are more likely to die if they live in a state or county with a high concentration of specialists (1). By contrast, living in a county or state with a high concentration of primary care physicians makes an American significantly less likely to die. As an illustration, imagine two hypothetical areas of a million inhabitants, identical except that one area has one hundred more practicing primary care physicians than its counterpart. Starfield's data suggest that the area with the additional hundred primary care physicians would have 346 fewer deaths per year.

These findings suggest that regardless of my fears of living among specialists, we as a society face a much bigger problem: the urgent need to train primary care physicians and raise the proportion of American medical students entering primary care. In a recent journal article, the American Academy of Family Practitioners (AAFP) expressed concern about the declining trend in family medicine residency positions filled with U.S. senior medical students (2). The AAFP is concerned because international students often return to their country of origin following training, and those who stay in the United States are less likely to practice in rural, underserved areas. Between 1998 and 2005, the article points out, the number of U.S. seniors entering family medicine residency programs has declined by 1,047.

There is no secret about the cause of this decline. In 1998, the average annual salary offer to a radiologist was only $57,000 more than that to a family practitioner. The latest figures show radiologists being offered $190,000 more than family practitioners. Small wonder, then, that diagnostic radiology has been one of the most sought-after residencies for American medical students in the past few years. This salary differential is only "one side of the coin." The other is the rising cost of medical education: one in twenty medical students has a graduating debt load exceeding $250,000.

As citizens concerned about limiting our own mortality, we need to dismiss our stereotypes of primary care physicians as the "gatekeepers" of '90s-era HMOs and accept the reality that many medical conditions are best diagnosed and treated by generalists. We need to recognize that the best way to keep from dying of gynecological cancer is early detection via annual pap smears and pelvic exams performed yearly by the same person, not by getting second and third opinions from gynecological oncologists after an emergency medicine doctor detects an end-stage symptomatic cancer.

Once we understand the value of having a good primary care physician, we need to use our power as consumers to choose health care plans that provide us with easier access to them. We need to let our elected representatives know that we support legislation subsidizing medical education and offering debt forgiveness to primary care doctors. If we recognize what's in our own interest and use our power as consumers and voters to influence the complexion of tomorrow's health care system, then there is hope for improvement. For my part, I'm hoping that some of Sinai's gynecological oncologists will find so much rewarding work providing female primary care that they won't bother renewing their specialty certifications. Then things may get a little safer around here.

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History and Health Care in Angola

Alexandra Leader, B.A. and Alexandra Snyder, B.A.

Health workers wear white, a symbol of witchcraft to Angolans in the area of Uige, where the Marburg virus ran rampant between early March and mid-July of 2005, killing a reported 312 people. This fact is symbolic of the problems in treating the disease, whose viral vector and reservoirs are unknown, but a clue to whose severity may be found in Angola's history. The failure of health care workers' efforts at controlling the virus' spread is unrelated to their herculean efforts, but seems rooted instead in Angola's history of subjugation to foreign interests and the devastating consequences of this history for Angola's people.

Angolans have reason to be suspicious of the arrival of foreigners. From the 15th century until 1975, Angola was under Portuguese control. For some 300 of these years, it served as a source of slaves for Portugal's principal colony, Brazil. The slave trade existed until the end of the 19th century, ending only in 1888. The slave trade era was characterized by constant armed conflict between native Angolans and the Portuguese colonialists; the Portuguese did not completely secure power until 1902. Following Angolan independence in 1975, most Europeans living in Angola left the country, taking their investments and technological knowledge with them, and leaving a collapsing local infrastructure in their wake. To compound matters, the Cold War powers filled the political vacuum in the 1970s and '80s, when the Soviet Union supported one political faction and the US, its opponents. The role of these powers subsided with the end of the Cold War in 1989, but fighting between the factions continued through 2002. This civil war has resulted in the deaths of an estimated one million Angolans, and refugee status for another million, out of a population of only 10.5 million (as of 2002).

Given this terrible population loss, superimposed on a lack of infrastructure and widespread poverty, it comes as no surprise that the Marburg virus went unrecognized, and was able to take hold in Angola, where infectious disease leads to the death of one in four children before the age of five.

Since local health care resources are inadequate, initially the task of fighting the virus fell to foreign health care workers, who, despite their best intentions and often the sacrifice of their lives, were unable to defeat the mysterious virus. Making their task even more difficult was the Angolans' fear of the health care workers themselves, which seemed in many cases to exceed their fear of the virus.

The Marburg virus has no treatment or vaccine, and no vector or reservoir has been established. All that is known is that it is spread via bodily fluids and can remain contagious for several days on contaminated surfaces outside the body. According to the international media, a deeply rooted and understandable suspicion of foreign intervention among many Angolans proved even more endemic than the disease. This fear may have been rooted in part in perceptions of bad patient outcomes: patients identified as infected were isolated and subsequently died 90% of the time, unable to contact their families. To health care workers, this process represents a successful step in preventing further spread of the virus. To the families of the deceased, this same procedure comes across as the death of a loved one at the hands of foreigners. Representative of this disjunction in interpretation, foreign health care workers noted that locals frequently hid sick relatives, and health care vans were attacked by angry townspeople armed with sticks, forcing health care surveillance teams to reluctantly designate certain neighborhoods as unsafe and their populations untreatable.

What should have been done and what can be done now about this tragedy? In stark contrast to Angola's past, the foreign presence, in this case health care teams, seem to have done everything possible to alleviate the epidemic, including efforts to identify the source of the disease, detect and prevent new cases through surveillance, care for the infected, and safely bury the dead. Sadly, in this case and others such actions may not be enough to overcome prevalent fear, a lack of resources and government inaction, all of which carry the weight of history. In theory, the Angolan government should have done more; it should have communicated information about the disease and about the vital efforts of the foreign health care workers to help the local population. Given Angola's troubled history and fragmented society, however, the government may have done all it could.

What can be done now? Perhaps the best solution would be for the foreign health care workers to begin training local Angolans in the detection and treatment of infectious diseases. Ultimately, these Angolans would provide basic health care to their own people, who would be more likely to trust them. The trainees would also be able to help foreign relief workers fight epidemics—and overcome the troubled legacy of the past. One positive outcome of the horrifying experience of the Marburg virus has been to set this process in motion. According to the World Health Organization, cooperation has occurred between local and international organizations, including education efforts involving traditional healers and community members. Ideally, such cooperation should be continued, and emulated in other locations where similar outbreaks are considered likely to occur, putting in place the informational infrastructure to prevent the transition from endemic to epidemic disease.

The Dangerous Betel Nut

Joyce Lo, B.S.

Imagine the scene: very young women wearing only lingerie perched on high stools in small glass booths that are peppered with flashing neon lights. The setting is not the red-light district of some city, but rather a busy road in Taiwan, where one may find many such booths intermingled with schools, businesses, and restaurants. Along with the flashing neon lights, these young ladies are intended to attract the attention of passersby and sell them boxes of betel nuts, an addictive stimulant similar in ways to chewing tobacco. Many of these "betel nut beauties," some of whom are minors, are aborigines who have been brought from their villages to the city to make money in this lucrative betel nut business.

Betel nut use remains a major, unresolved public health issue in Taiwan. While Taiwan may be unique in the way that betel nut is sold, betel nut is in no way unique to Taiwan. Derived from seeds of the areca palm, betel nut is chewed regularly by at least 10% of the world population, and is the fourth most commonly used drug. Although betel nut (and its additives) is well-known to be carcinogenic and is a key risk factor for the development of oral cancer, esophageal cancer, and a myriad of dental and oral hygiene problems, the government and general public have done very little to curb its wide use and availability. Moreover, there is a major lack of action and interest in educating the public, as compared to the efforts made in educating them about the dangers of other addictive drugs such as tobacco, alcohol, marijuana, and ecstasy.

The inaction of the Ministry of Health and other government health agencies leads one to believe that they assume the betel nut issue to be unimportant. This, however, could not be farther from the truth. Case-control studies carried out by medical universities in Taiwan have demonstrated that those who chew betel nuts have a 24-times greater risk of developing esophageal cancer and a 28-times greater risk of developing oral cancer than non-users. Within Taiwan, oral cancer is the fifth leading cancer in incidence and the sixth in mortality among males, and at least 80% of these deaths are associated with betel nut use. Experts have estimated that about 88% of oral cancer and 96% of mucous membrane fibrosis patients in Taiwan are habitual betel nut chewers. Furthermore, recent studies at Kaohsiung Medical University, in Taiwan, indicate that betel nut use also increases the risks of miscarriage, stillbirth, and infant underweight birth by three to five times.

Perhaps government officials are willing to overlook the dangers of betel nut use because of the extensive lobbying by betel nut farmers to prevent more government involvement in the prevention of sales. Even though betel nuts are also imported from Southeast Asia, they are Taiwan's second largest agricultural crop, and many farmers subsist on it alone. At the American Association for Cancer Research, it was reported that from 1981–2000, a huge increase in oral cancer among Taiwanese men paralleled a nearly sevenfold increase in Taiwan's production of betel nut.

While betel nut usage is most common among middle-aged and elderly men, today's aggressive marketing techniques are appealing to adolescents. And although the image of betel nut chewing is considered unattractive by some young people because of the discolored teeth and gums that result and the spitting of red juices into the street, the latest trend of using sex to sell it is beginning to attract more and more young adults and teenagers to the product. In the eight years that I have been living in Taiwan, the audacity of betel nut sellers has increased dramatically, culminating in the marketing strategy that creates a highly visible, roadside "strip show." Even more alarming is that data from case-control studies have showed that adolescents who use betel nuts are much more likely to begin experimenting with methamphetamine and other drugs than are non-users.

I believe that government and health officials need to take a more active role in informing the public of the dangers of betel nut use, and also help restrict its availability to young people. Strategies now being used to decrease smoking, underage drinking, and recreational drug use should also be employed to cut betel nut use. These strategies should include both public education and support services. In addition, stricter laws need to be passed and implemented to prevent minors from purchasing betel nuts and to penalize adults who purchase them for minors. Action should also be taken on the side of the betel nut farmers and distributors. The Taiwan government should consider offering incentives to encourage farmers to diversify their crops and to decrease their reliance on betel nut as a crop. Betel nut sellers should be required to modify their current marketing campaign so as not to exploit women or use the image of sex to sell a harmful drug. Sellers should also be required to identify on their packaging the risks associated with use of their products.

Government and general societal tolerance of the aggressive sales techniques employed by betel nut sellers gives people the dangerous idea that betel nut use is an acceptable part of Taiwanese culture. If that idea could be changed and if Taiwan's farmers were encouraged to begin planting other crops, Taiwan could become a much healthier place.

They Suffer in Silence

LEIGH MARTINEZ WRIGHT, B.A.

THEY SUFFER IN SILENCE, sometimes before our eyes. People who once cared for us, educated us, guided us along life's difficult path are now on a difficult journey of their own. In a society obsessed with youth, it is not surprising that our elderly population is often overlooked, forgotten and—in too many cases—abused.

Elder abuse can take many forms and may manifest itself as physical abuse, psychological abuse, financial exploitation, or mere neglect. It can be active—physical harm to the elderly individual—or passive: withholding medications or hygienic care. While often brought to the public's attention as a problem confined to nursing home residents, in reality elder abuse is a sustained pattern of maltreatment that often occurs between the elderly individual and a person with whom they have an ongoing relationship—son, daughter, neighbor, spouse, caregiver—anyone may be a perpetrator. Frequently, the victim is isolated, intimidated, ashamed and fearful of retribution. It is estimated that only one in fourteen incidents of elder abuse is reported to the authorities and—more disturbingly—that between one and two million of our parents, grandparents, friends and neighbors become victims each year.

As a public health issue, elder abuse should be a growing concern to all of our citizens. In August 1998, the *Journal of the American Medical Association* described the first study that compared the mortality of mistreated elderly individuals with those who had not been mistreated. Even when confounding factors such as chronic disease and socioeconomic status are taken into account, abuse victims in similar populations were three times more likely to die than their non-abused counterparts. The most rapidly growing demographic in the United States consists of older Americans. By the year 2050, it is expected that more than 20% of the American population will consist of older individuals; the number of abused citizens is expected to grow in proportion to this increase. Victims of elder abuse make twice as many visits to medical facilities, have higher outpatient expenses and are more dependent on federal health care programs than their non-victimized counterparts. Thus, their increasing numbers can be expected to place added strain on an already overburdened American health care system.

The federal government's response to this issue can only be characterized as one of inaction. Despite a robust response when the issue was first raised in congressional hearings twenty-five years ago, to date no federal regulations have been promulgated that deal with what was once described as a "disgrace" and a "burgeoning national scandal." State agencies were quick to respond to the issue, enacting numerous laws and programs to identify and combat the problem. However, chronic underfunding of state elder abuse programs has led to an inconsistent patchwork of statutes that vary by state and, more important, authorize limited resources to assist the victims. To see an example of federal legislative neglect of the issue, one need look no farther than the Elder Justice Act (Senate Bill 333). Introduced by the now-retired Senator John Breaux in 2003, this bill aimed to coordinate the activities of the Department of Health and Human Services, the Department of Justice and other federal, state, local and private agencies, to deal with the problem of elder abuse, neglect and exploitation and provide federal leadership and guidelines for state agencies dealing with elder abuse issues. If passed, this bill would have provided $650 million a year for seven years to fund adult protective service agencies. Yet, despite bipartisan support, the Elder Justice Act was not passed by the close of the 108th Congress last year. (No further action has been taken this year.) State and community agencies are struggling to care for the elderly victims who are reported to them each year, but it may be up to the federal government to pass the legislation that will effectively coordinate and adequately fund their efforts.

No truly ethical person approves of elder abuse, but it is a problem we often—for various reasons—find easier to overlook than to solve. Our lack of action to protect these vulnerable members of our society may be a manifestation of how we as a society treat our elders. It is a problem that we—socially and morally—will eventually have to deal with.

Breastfeeding Makes for Better Health

LAUREN SCHIFF, B.A.

HEALTH CARE PROVIDERS in the United States are struggling to contend with an overwhelming number of health epidemics: obesity, type II diabetes, hypertension, and cardiac disease, among many others. These health conditions are causally intertwined with one another and dependent on American cultural and socioeconomic factors. Preventive health care offers a hope of reducing the risk factors that lead to these systemic diseases. And among these risk factors is the use of infant formula for newborns. It is imperative that new mothers be strongly advised to breastfeed for at least the first six months, to protect their infants from the possible harmful effects of formula feeding, and provide them with the long-lasting health benefits of mother's milk.

In 1981 The World Health Organization (WHO) issued "The International Code of Marketing of Breast Milk Substitutes," which outlined strict restrictions on formula companies' marketing strategies, including "no promotion of products in health-care facilities," and "no...idealizing [of] artificial feeding." Underlying these restrictions was conclusive medical research that breast milk substitutes lack the necessary nutritional elements for proper infant growth and development and can contain contaminants such as aluminum, lead, and iodine.

Since the WHO's initial campaign, continued medical research has found further negative correlations between formula use and desirable health outcomes. Of primary interest, in light of the obesity epidemic plaguing the United States, is that multiple cohort studies have found that formula feeding is associated with increased adiposity both during the first two years of life, and throughout adolescence. Conversely, breastfed infants show an increased adiposity within the first four months of life followed by a marked decline through adolescence and adulthood.

In addition, a number of studies have shown that infant formula use is correlated with a significantly increased risk of allergy and infection in infancy. It is well known that breast milk confers immune antibodies to a suckling infant for the first three months of life, during which time the infant's own immune system is not yet sufficiently active. Therefore, as these studies demonstrate, lack of maternal antibodies results in increased opportunistic infection, including otitis media, pneumonia, bacteremia, urinary-tract infections, meningitis, bronchitis, and respiratory infections. Furthermore, because colostrum acts to stimulate neonatal gastrointestinal maturation and high levels of IgA (the antibody responsible for gut immunity), formula-fed infants have been shown to have a high incidence of gastrointestinal infection. A number of studies have also suggested that early exposure to cow's milk and substitute products may cause increased risk for allergies such as eczema, asthma, rhinitis, and food allergies. On the contrary, breastfeeding has been shown to have a protective effect against the onset of chronic illnesses such as type I diabetes mellitus, cancer and lymphomas, Crohn's disease, and celiac disease.

It must be noted, however, that in the majority of studies in which these correlations were found, the best health outcomes were seen in babies who were breastfed continually for the first 6–13 months, without intermittent substitute with solid food or formula. Increasingly improved health outcomes were similarly seen with increasing reduction in formula and solid food feeding. Therefore, there appears to be a dose-response scale of improvement.

An important effect of the marked decrease in these formula-associated health risks is an overall reduction in hospital admissions among breastfed children. This may significantly reduce health care costs to both health care providers and insurers as well as to the individual mothers. Breastfeeding is a low-cost feeding method that reduces health care utilization. Moreover, it has been shown that breastfeeding enhances the mother-baby bond and thus may decrease the mother's risk of depression and anxiety. Just as with most preventive health care strategies, encouraging breastfeeding among new mothers does require preliminary education by health care staff; it also requires a home support system to help the mother maintain prolonged breastfeeding practices.

Despite the convincing evidence in support of breastfeeding, the advertising power of formula companies has proven that preventive health care must vigorously promote the breastfeeding initiative: Several formula companies, including Nestlé, have been found to be in violation of the WHO code, and many new mothers continue to opt for formula feeding due to the influence of corporate advertising. Of particular note was Nestlé's advertising campaign within developing countries; it touted formula feeding as a healthier alternative to breastfeeding. Although Nestlé has since withdrawn that particular advertising message, they continue to ignore the WHO code, and as recently as 2000, were cited for improper marketing practices. The effects of their practices are not insignificant. Mothers throughout developing countries were found to be mixing Nestlé powder formula with the (only available) contaminated water. Furthermore, in order to save money, mothers diluted the formula, thereby unintentionally malnourishing their children. Although it may be argued that companies such as Nestlé are not responsible for educating the public about their products' proper uses and indications, I would suggest that the AIDS epidemic has indeed made this an obligation: Since breastfeeding is contraindicated for HIV positive women, the onus is upon formula companies to provide widely accessible, low cost, sufficiently fortified formulas with extensive bottle feeding instructions, a measure that may curtail such high transmission of HIV from mother to infant in developing countries. Incorrect use of infant formula, however, is a significant problem not only in developing countries. Because companies such as Nestlé simply equate infant formula with natural breast milk without providing sufficient education on its proper use, mothers in Western countries incorrectly reconstitute formulas, overheat formula in the microwave, inflicting mouth and throat burns, and may induce aspiration by incorrect bottle positioning.

In light of the overwhelming body of literature that illuminates the health-protective benefits of breastfeeding and the significant health risks associated with formula feeding, it is crucial that new mothers resist the enticing advertising of formula companies and adhere to the much healthier regimen of breastfeeding. If a significant increase in uninterrupted breastfeeding practices can be achieved in the United States, perhaps we will also see a reduction in childhood obesity, opportunistic infection, and acquired allergies.

Commentary

I Matched, Not for Residency, but to Save a Life

JASON AARON SOKOL, M.D.

AS AN INTERN, it is easy to get caught up in the tedious everyday tasks of drawing blood, and checking lab results, repleting electrolytes, writing notes, calling consults, restarting diet orders, answering endless pages, etc. The repetitious nature of an intern's day can easily cause him or her to forget the original reasons for choosing this life.

After 4 months of this routine, I took a brief vacation. On my return, I discovered that I had a voicemail from an organization called the Gift of Life. As I listened to the message, I was stunned. "Hi, Jason. This is the Gift of Life calling. You might remember registering 9 months ago with us.... Please call us back.... It seems that you are a possible match."

A match! I couldn't believe it. I remembered registering with my wife one Sunday at a local synagogue for a bone marrow drive. I never thought I would ever actually be called, and certainly not this quickly.

I sat alone with my thoughts before calling back. Who could it be for? Would it hurt? Would I be able to find someone to cover me at the hospital? I thought about the person who needed my bone marrow and how he or she must feel: alone, scared, hopeful. I then thought about how I would feel if I were the one who needed the transplant, or if a family member or friend needed one. I immediately made the decision to help this person. The message reminded me of the reason I had become a doctor—to help people—and I recalled the Talmudic saying that so often echoes in my mind: "He who saves one life, it is as if he saved the entire world."

I picked up the phone and returned the call. The representative said, "Jason, you are one of four possible matches for a 26-year-old male with a recurrent lymphoma or leukemia.... That is all I can tell you." After unofficially accepting, I got another call a day later: "Jason, it turns out that you are the closest match compared to the other people. We don't have to do any further testing." I soon learned that a simple swab of my mouth had revealed a close genetic match. A simple "yes" on my part started the healing process.

Sadly, thousands of adults and children are diagnosed with blood-related cancers such as lymphoma and leukemia every day. The International Bone Marrow Transplant Registry reports that in 2002, approximately 20,000 transplants were performed in North America. Of the 7,200 allotransplants performed, more than 5,000 were for leukemia or myeloproliferative diseases. Worldwide, more than one-third of allogenic transplants are from unrelated donors (1). The National Marrow Donor Pool registry has over five million volunteer donors and performs more than 170 stem cell transplants a month. Many people in need of a transplant are unable to find a family member who is a suitable match, and must seek an unrelated volunteer donor through an international network of registries called Bone Marrow Donors Worldwide.

I registered with the Gift of Life Bone Marrow Registry. Gift of Life was created following extensive donor recruitment for Jay Feinberg, a young man who was dying of leukemia. It was the very last volunteer who turned out to be a match and saved Jay's life. Since 1991, almost 150,000 volunteers have registered with the Gift of Life. All bone marrow registries are linked anonymously statewide, nationally and internationally.

The first step of my donation process was deciding to go to a donor registration center in New York City. Registration included taking a Q-tip

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swab of the inside of my cheek; as an alternative, I could have given a blood sample. The tissue is then human leukocyte antigen (HLA) tested and its characteristics anonymously entered in a worldwide transplant registry. Every volunteer remains in the registry until the age of 61. Once identified as a potential match, the donor is asked to pursue further blood testing for "confirmatory typing." He or she is provided with additional information and given a complete physical examination.

Traditionally, we are taught about the painful process of donating bone marrow. As a recent graduate from medical school, I was aware of the possibility of donating bone marrow through peripheral blood. I soon learned that after receiving 5 Neupogen® injections, I could donate through peripheral blood stem cells (PBSC).

Traditionally, bone marrow donation takes place in an operating room setting, under local or general anesthesia. Using needle aspiration, bone marrow is taken from the iliac crest. Compared to the traditional method, the PBSC procedure is less invasive. I was offered and opted for PBSC. This procedure involves receiving daily Neupogen® injections for 5 days. The Neupogen® essentially mobilizes stem cells from the bone marrow to travel into the peripheral blood. There are some side effects, including flu-like symptoms and bone pain, but they usually disappear after the stem cells are donated. The actual donation is done immediately after the last Neupogen® injection. For 4–6 hours, the blood is filtered through a cell-separating machine, a procedure called apheresis. Upon completion, I was able to write a card to my anonymous recipient. And so, with wishes of luck and a speedy recovery, a courier took my stem cells to their recipient.

Prior to receiving the transplant, the recipient undergoes intense radiation therapy and chemotherapy to eradicate the malignancy. The patient then receives the stem cells intravenously; they migrate to the bone marrow and hopefully engraft to produce healthy cells.

Anyone can register with the National Marrow Donor Program® (www.marrow.org) or the Gift of Life Bone Marrow Registry (www.giftoflife.org). We, as members of the medical profession, should challenge ourselves to go beyond the Hippocratic Oath that we pledged and take part in this exciting, life-saving experience.

Each month I look forward to a call from the Gift of Life updating me on my anonymous recipient. The most recent update informed me that my recipient is in 100% remission, with 100% of my cells and no evidence of graft-versus-host response. Whoever you are, I wish you, and all recipients, the best of luck and a successful recovery. I am honored and fortunate that I was able to give you a second chance at life. I want to thank the Gift of Life, my colleagues at Mount Sinai, the doctors and nurses at New York Presbyterian, my family and my wife for being supportive and covering for me, and for making it possible for me to donate. It is an amazing feeling to know that a person is doing well with my cells. I would definitely do it again. And I believe most people would find it as rewarding as I have.

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In Memoriam

Leonard I. Malis, M.D.

1919-2005

On September 12, 2005, Mount Sinai lost one of its pioneering giants, Dr. Leonard I. Malis. Dr. Malis was born in 1919 in Philadelphia, and grew up in Atlantic City, NJ. His technological talents appeared early. At age 12, he was one of the youngest licensed ham radio operators in the United States. By 15, he had designed and built a 1,000-watt transmitter, which allowed him to talk with fellow enthusiasts around the world. At 16, he was repairing pinball machines and "take-your-own-photo" booths for boardwalk amusement arcades, and slot machines for local gambling casinos.

At the University of Virginia, as part of the Department of Biology honors program, he designed and built his own laboratory equipment—radiowave generators and special optical, photographic, thermoregulatory, and light systems. He also studied the effects of radiation on cellular mechanisms and devised a binocular stereoscopic dissecting microscope that would pave the way for future developments in microneurosurgery.

During World War II, Dr. Malis served as a captain in the Medical Corps, where he became head of a neurological unit. After the war, ten months as a general practitioner ("an invaluable learning experience and the unhappiest time of my life") preceded his neurology residency with Dr. Israel Wechsler at The Mount Sinai Hospital. Training in neurosurgery followed under Dr. Ira Cohen, who encouraged the development of full-column myelography. Using this technique, Dr. Malis clearly demonstrated disc herniation, intramedullary and extramedullary neoplasms, and spinal structural abnormalities.

In 1950, the Dazian Foundation supported his fellowship year at Yale in the laboratory of John Fulton, the eminent neuroscientist. While his primary research at Yale was in neurophysiology, Dr. Malis also achieved advances in neurosurgery and neuroradiology. The monopolar Bovie electrocautery, with improper grounds, charring, and high impedance, was replaced by his new spark-gap bipolar forceps, an indispensable tool for pinpointing hemostasis in microsurgery. He also designed a serial cassette changer to replace the single-cassette technique then in use for cerebral angiography. The prototype machine, completed at The Mount Sinai Hospital in 1951, produced over 250,000 stereoscopic views of the intrinsic vasculature of the brain, before being retired.

When Dr. Malis returned to Mount Sinai, his electrophysiology laboratory was on the sixth floor of the old surgical pavilion. There, Dr. Malis regularly employed an operating microscope for a full range of animal experiments. All of his microsurgical instruments, oscilloscopes, automatic camera systems, physiological amplifiers, and electronic stimulators were put together in his basement workshop.

Demands on a full-time attending neurosurgeon, who was now authoring numerous publications in basic science and clinical research, were occasionally interrupted. Research into the extensive sensory cortex of the dolphin, to map the areas involved in vocalization, required a trip to St. Petersburg, Florida, and transport of Dr. Malis' entire Mount Sinai laboratory. The newly available 60-inch cyclotron at the Brookhaven National Laboratories stimulated him to construct a special gun-sight device that aligned a proton or deuteron beam and focused ionizing radiation on specific tracts of the cat brain. The hundreds of lesions created provided the earliest information on neuronal and glial radiosensitivity.

Until 1965, regular operating room use of the binocular surgical microscope was confined to otolaryngology procedures. While operating on a child with a large craniopharyngioma, Dr. Malis found a fixed optic chiasm with only enough room for a minimal biopsy without damaging the carotid artery. He borrowed the binocular microscope and, using his own animal laboratory instruments, accomplished complete excision of the tumor. By 1968, he had adapted the same model television carried on NASA moon missions, so that residents and operating room staff could simultaneously follow his microsurgical procedures to clip aneurysms, ablate arteriovenous malformations, and totally remove acoustic neuromas—a neurosurgical feat that Harvey Cushing had thought impossible. Not content with this initial success in "telesurgery," he established audiovisual connections to Neuropathology, Neuroradiology, and the Office of Neurosurgery, so that immediate consultation and communication with other professors became available. His inventiveness included running the needed cables between buildings by fly casting at night to avoid scrutiny.

The first microneurosurgical course in the United States was held at The Mount Sinai Hospital after Dr. Malis convinced the Zeiss Corporation to hold all microscope deliveries for three months so that 40 operating microscopes would be available for the program.

In 1970, Dr. Malis succeeded Sidney Gross as professor of neurosurgery and chairman of the department, at The Mount Sinai Hospital. The next two decades saw his Department of Neurosurgery achieve world-class status. Patients from all over the United States and abroad sought out Dr. Malis' expertise in spine and brain disorders. Treatment of herniated lumbar and cervical discs, skull-based tumors, and carotid aneurysms, along with middle cerebral-external carotid anastomoses, cerebrospinal fluid shunts, and cortical electrode placements, were included in the more than 300 operations performed each year. Each of his forty residents became board certified and went on to academic positions and successful practices. Innovations in microneurosurgery, neuroradiological technique, critical care, antibiotic prophylaxis, operative microphotography, and electroneurophysiology became the subjects of numerous journal articles and textbook chapters. Dr. Malis' academic appointees presented papers frequently at New York City, New York State, and national neurosurgical scientific meetings.

Everyone who worked with, learned from, and operated with Dr. Malis was aware of his unique abilities—including ambidexterity and the ability to envision neuroanatomy in three dimensions. His staff watched in awe as he drew (left and right with both hands simultaneously) the axial images of his patients' X-rays long before the advent of CT scanning. Dr. Malis' warmth as a mentor and his kindness to patients in distress were just as apparent as his genius for problem solving.

Leonard Malis' influence will endure. His numerous insights and innovations helped shape modern medicine and inspired many of those who will build its future.

He is survived by his wife, Ruth, whom he met while he was in medical school, two children, Larry and Lynn, three grandchildren, and a brother, Jerry.

Martin H. Savitz, M.D., Ph.D.
Assistant Editor
The Mount Sinai Journal of Medicine

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1. Brown LK. Sleep apnea syndromes: overview and diagnostic approach. Mt Sinai J Med 1994; 61:99–112.

2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309–315.

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THEME ISSUE

Issues in Medical Ethics

Special Challenges in Pediatrics

Kurt Hirschhorn, Ian R. Holzman, Daniel A. Moros, Rosamond Rhodes, guest editors

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Issues in Medical Ethics:

Special Challenges in Pediatrics

SINCE THE END OF WORLD WAR II, the ethical issues that arise in modern medicine have grown more and more complex and challenging. As a result, an entirely new field of study, called medical ethics or bioethics, has emerged. Or rather, it has been created by the ethicists and clinicians who frequently wrestle with medical problems and seek to share their insights with patients, their families, other medical professionals, policy makers and laypersons who feel the need for guidance in resolving the ethical questions posed by modern medicine.

To a great extent, the morally demanding questions of bioethics are related to medicine's rapidly evolving technology. Clearly, that technology has provided medical interventions that can prolong life and can also provide a good deal of information about people's current health and their predisposition to future diseases and disability. Yet both the interventions and the information raise challenging ethical issues. Should life always be extended? Do some burdens and some costs make life extension immoral or unreasonable? Is there some information that we are better off not knowing? And always, who should make the decision for whom? Sometimes it is extremely difficult to formulate clear answers to such questions. And even when some authorities seem confident about their answers, their answers may disagree with those of other authorities. People often feel passionately about their own positions and just as passionately about the stands of those who hold opposing views.

As difficult as it is to arrive at near certainty or even consensus in medical ethics, the level of controversy rises dramatically whenever children are involved. People tend to call for a high level of protection for children; they recognize a social duty to promote their good and protect them from harm. For this reason, it is almost expected that clinical decisions involving the lives and futures of children will become charged with emotion and controversy.

In addition to our protectiveness with regard to children and the moral ambiguity of the medical decisions that have to be made, two characteristics of children make ethical decisions in pediatrics more difficult than in other areas of medicine. One is that they are younger than adults. Children who survive a health crisis are, therefore, likely to live with the consequences of the medical decisions for a relatively long time. Also, because of their size and their stage of development, medical interventions may have more beneficial or harmful effects on them than they might have on adults. (It is also true that, because of their plasticity and resilience, children can sometimes overcome injuries that would devastate an adult.)

Children are different from most adults in that they lack the capacity to make autonomous decisions about their own medical care. This legal incapacity is based on observable fact. Very young children are not able to make any decisions at all. Older children may sometimes be able to understand their situation and the choices that have to be made, but their thinking is different from mature thinking in numerous respects. The young tend to think of themselves as immortal and invulnerable, they tend to focus on short-term consequences and ignore or undervalue more distant effects, they fail to make subtle but significant distinctions, they tend to give great weight to the projected opinions of peers, and they tend to behave in ways that oppose the conclusions of their own reflection.

In addition to these factors, the place of parental authority complicates the ethics of pediatrics. For the most part, our society allows parental discretion a wide latitude. Parents have great freedom when it comes to naming their children, deciding whether or not they will have a religious education, where they will live, and which of their talents will be nurtured and which activities they will pursue. Parents are also allowed the freedom to choose the kinds of food their children will eat, the education that they have, and the medical and dental care that they will or will not receive.

At the same time, other people in society, such as teachers and physicians, are assigned some responsibility for the welfare of children who come to their attention. And their responsibilities may clash with the rights of the children's parents. Parents and pediatricians may find themselves in situations where they strongly disagree about whether a course of treatment will be good for a child and also about whether a child has decisional capacity. In addition, the child may have his or her own strongly held view, and there may be no incontrovertible way to determine which party is right or even if any is wrong.

The papers in this issue of *The Mount Sinai Journal of Medicine* address some of the difficult ethical dilemmas that arise in the care of children. The authors bring to bear insights they have developed through years of work as clinicians and ethicists. They offer conceptual frameworks that can be put to use in addressing a range of similar circumstances. Arthur Kopelman, Linda Siegel and John Lantos each address aspects of the controversial ethical issues in situations where a child's life can be prolonged, but at a significant cost, and when the medical professionals and family members have different views about what should be done. A team from the Mount Sinai Adolescent Health Center—Daniel Summers, Ivanya Alpert, Thaina Rousseau-Pierre, Mara Minguez, Simone Manigault, Sharon Edwards, Anne Nucci, and Angela Diaz—consider some of the moral questions about benefit, decisional capacity, parental discretion, and law that arise in the context of providing care for adolescent patients. Loretta Kopelman addresses questions of risk, harm, and the need for knowledge in the context of research that involves children. Mary Kay Pelias and Rosamond Rhodes consider the moral issues involved in designing policy to govern the testing of children for adult onset genetic diseases that are not readily amenable to prevention or treatment. Taken together, this collection of papers seeks to advance our understanding of the challenging ethical issues in pediatrics.

Understanding, Avoiding, and Resolving End-of-Life Conflicts in the NICU

Arthur E. Kopelman, M.D.

Abstract

Parents and health care professionals may disagree about whether to continue or discontinue life support for infants in the neonatal intensive care unit (NICU) when the infant has an extremely poor chance of survival and/or probably has profound neurological damage. Conflict usually occurs when the parents want everything possible done to keep their infant alive, while the medical team believes that continued care will only prolong suffering and consume resources needed for other patients. The argument is made that often insufficient time and effort is made to fully understand the parents' reason(s) for requesting continued life support. Instead, they are advised to stop support, the advice is rejected, and this results in conflict with the family.

A case is used to illustrate this situation, and five typical reasons families have for requesting continued life support, against the advice of the infant's physician, are presented. Each reason needs to be explored and addressed differently. Full appreciation of the reason for the family's request can often prevent conflict between the physician and the family and replace it with support and understanding. Increased emphasis on educating physicians about how to conduct end-of-life discussions, making time for repeated family conferences, and use of a palliative care consultant, should be considered as ways to improve family-physician communication and prevent unnecessary conflicts.

Key Words: End of life, premature infant, communication with families, futility, inappropriate medical care, best interests, ethics.

Eighty percent of the deaths that occur in the neonatal intensive care unit (NICU) are preceded by decisions to limit, withhold, or withdraw life support because the prognosis for survival and/or a meaningful quality of life is extremely poor (1). Availability of powerful technologies that may save lives or only succeed in greatly prolonging dying makes it essential that families and physicians evaluate whether continuation of such therapies is in the best interest of an infant whose prognosis is extremely poor. If patients are or have been competent, their own judgments are used to determine their end-of-life care. However, the infant's interest is best served when the parents and physicians can agree about what therapeutic goal is appropriate for him, and that goal is then used to guide therapy.

Conflicts between families and medical caretakers about whether to escalate, continue, or discontinue life support for critically ill infants are not uncommon. Most often conflict arises in situations where the prognosis is extremely poor and continued survival depends upon therapies that may cause discomfort or suffering. In these conflicts, members of the health care team may believe that life support should be stopped, but the family disagrees and wants full support continued. The family wants to keep the infant alive at all costs, while the medical team believes that such care will only prolong discomfort for a dying or profoundly disabled infant and waste scarce medical resources. As conflict continues, both the family and members of the medical team experience significant distress or anger, which exacerbates the problem of poor communication.

Disagreement and conflict about end-of-life issues often result from inadequate understanding of the family's rationale by the medical team, and consequent disagreement between the family and medical team about the goal of treatment (2, 3). Frequently, these conflicts result from inadequate communication by the medical team (4). What follows is a case presentation that demonstrates how such miscommunication may rapidly lead to conflict and tension between the family and the medical team. Also presented are five typical reasons given by parents, in the author's experience, for

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requesting continued life support for infants when the medical team believes it is inappropriate. The article attempts to show how understanding the family's reasoning in each situation might have informed the discussion and prevented or lessened conflict. There have been recent efforts made to find legislative or judicial solutions to resolve these conflicts. Using these sorts of measures for conflict resolution may on rare occasions be necessary as a last resort, but doing so is likely to be costly, time consuming, and emotionally painful, and may not succeed in resolving the conflict. It is the thesis of this article that improved communication with families can avoid many end-of-life conflicts.

Case: A Family's Demand for "Inappropriate Care"

A 520 gm (1 pound 2 ounce) Caucasian infant was delivered vaginally at 23–24 weeks' gestation by an 18-year-old unmarried woman. The infant's mother was healthy except for being obese. She had not known she was pregnant and had not received prenatal care. She was a high school student, and lived with her mother. She was still seeing the father of the infant, but they were not "going steady." After experiencing abdominal pains she had gone to the emergency department of her local hospital, where she delivered within a few minutes of arrival. The infant was intubated after several attempts and was then placed on a ventilator. He had Apgar scores of 2, 4, and 7 at 1, 5, and 10 minutes. Soon after birth, the infant was transferred by helicopter to the regional level 3 NICU.

On arrival at the NICU the infant was hypothermic and hypotensive, and was put on high ventilator settings. Umbilical artery and vein catheters were placed, and over the first two days he was treated with two doses of surfactant for respiratory distress syndrome, given indomethacin to close a patent ductus arteriosus, and treated with pressors for hypotension.

On the third day the infant had repeated generalized seizures and was unresponsive to pain. An ultrasound study of the infant's brain showed a large right-sided "grade 4" intraventricular and parenchymal hemorrhage (venous infarct). The neonatologist discussed the infant's prognosis with other members of the clinical team, including pediatric residents, the bedside nurse, the social worker, and a second neonatologist. In light of the cerebral hemorrhagic infarct and the neurological picture, they concluded that the infant now had less than a 10% chance of survival to discharge, although death did not appear to be imminent if full support was continued. Also, if the infant did survive, there was a 90% chance of severe-to-profound neurological damage with likely mental retardation, developmental delay, and cerebral palsy. An infant born at such an early gestational age was also likely to develop retinopathy of prematurity, with a moderate chance of reduced visual acuity or blindness.

All of these outcomes were probabilities, of course, and not certainties. While 90% of such infants die, some do survive, and while most survivors have serious disabilities, 10% do not have developmental or neurological problems. The presence of retinopathy of prematurity (and possible blindness) could not be evaluated before 6 weeks, and the earliest meaningful evaluation of the infant's developmental status would be at 6 months of age. If the medical team and the infant's mother agreed to discontinue life support at this time (i.e., day 3), the infant would soon die. But if it was decided to defer such a decision for 6 weeks until the infant's neurodevelopmental status and prognosis for vision could be better evaluated, the infant might die while receiving full life support or else he would no longer be dependant on a ventilator for survival.

The infant's poor prognosis for survival, and the likelihood of serious developmental problems if he did survive, were discussed with the infant's mother and the maternal grandmother. After several meetings it was suggested to them that discontinuation of life support be considered because further care was likely to be futile, and because in the unlikely possibility that the infant did survive, he would probably have a very poor quality of life. But the mother replied that she wanted everything possible to be done for her son.

After the family asked that full life support be continued despite the team's recommendation that it be stopped, the physicians and nurses became extremely frustrated, for several reasons. The staff didn't think that the family appreciated how burdensome continuing care was for the infant, and they believed that the infant would probably die despite continuing ventilator support. The nurses perceived that the infant was suffering, and they resented having to care for him 24 hours a day, while the family only paid occasional brief visits. Some nurses said that they felt the family was forcing them "to torture the infant" by continuing pointless care. Others questioned whether the family understood what the infant's life would be like if he survived with severe disabilities such as developmental retardation, cerebral palsy, and blindness. Subsequently, a number of nurses asked not to be assigned to the infant. The family quickly sensed the staff's disapproval and lack of support.

Rather than repeatedly face the disapproving atmosphere, critical comments, and pressure to discontinue life support, they visited less and less often, and only at night, when the attending neonatologist was not present.

In the situation described, which is not atypical, an impasse had already been reached. Communication with the family had become poor and was not likely to improve. And neither the staff's disapproval of the family's request for continued treatment nor their pressure on the family to change their mind was likely to change the situation. Staff members discussed among themselves whether to consult the hospital ethics committee, to help persuade the family to do what was "ethically correct," or to ask the courts to take custody from the family because of their "inappropriate" decision for the infant. While such discussions were understandable given the frustration felt by the staff members, there was little chance that an ethics consultation would have helped improve communication, and legal action was unlikely to resolve the conflict anytime soon. However, the impasse might have been avoided entirely if the attending neonatologist had taken time to understand the family's thinking before suggesting that life support for the infant be stopped. This could have been achieved by clearly stating the prognosis repeatedly, and then asking the family for their reaction or response without first making a recommendation to them. This process sometimes takes several meetings, since the family needs time to process the information.

Some Parents' Perspectives

Here are five reasons given to the author by different families requesting continued life support for their infant, when the medical team believed such requests were inappropriate:

1. They believed that the infant could survive and was likely to be normal or to have only mild learning problems.
2. They believed that God performs miracles, and a great many members of their church were praying for their infant to survive and be normal. They felt that if they agreed to limit or stop life support, members of their church would see them as lacking faith in God's ability to heal.
3. They knew of similar cases in which the doctors' predictions were wrong. Also they suspected that their infant might not be receiving the best possible care, because they were poor and on Medicaid.
4. The mother saw survival of her infant as the only solution to a life crisis. One such mother had been depressed, and her boyfriend was the only person she felt close to. She believed he would remain with her if their son survived, but would leave her if their infant died.
5. The likelihood of the infant having moderate-to-severe disabilities was not important to them. They believed that the life of every child, even one with severe or profound disabilities, had great value and should be saved. They were prepared to commit themselves to raising him if he survived, regardless of his limitations.

Discussion

If the members of the health care team had taken the time to fully understand the family's reasons for asking that life support be continued, they might have done a better job in helping them deal with a tragic situation, and the conflict might have been prevented entirely. Let us look at each of the five reasons that families might give for requesting continuation of life support for their infant, when the staff felt the request was inappropriate, and consider in each instance what approach by the physician might have been helpful (Table 1).

They believed that the infant could survive and was likely to be normal or to just have mild learning problems.

In this case (the case presented in this article) the family simply misunderstood what the prognosis was for the infant. This may seem unlikely, as the neonatologist had told them clearly in several meetings that the infant would probably die, and that if he didn't, he would most likely have severe-to-profound neurologic disabilities. Yet studies have shown that it is quite common for families to misunderstand the information provided to them by physicians (4). Often this occurs because of the extreme stress and anxiety that they feel, or because they don't understand the medical terminol-

TABLE 1
Reasons That Some Families May Demand Apparently "Inappropriate Care"

Failure to comprehend prognosis.
Religious beliefs about end-of-life decisions.
Religious belief in miracles.
Lack of confidence in medical diagnosis or prognosis.
Belief that more can be done.
Secondary gain.
Disagreement about seriousness of outcome.

ogy or the concepts being presented. The infant's mother may have been "in denial," because she hadn't even known she was pregnant until the baby was born. She may also have felt tremendous guilt because she hadn't received prenatal care.

Medical terminology can also become a barrier between physicians and laypersons; it is important to use language that people understand. The terms "profound neurological disabilities" or even "brain damage" may not convey a picture of the infant's future as clearly as saying that the infant will never walk or talk, or know his family. Also, concepts such as percentage probabilities, which seem straightforward to members of the medical team, may be incomprehensible to someone who isn't familiar with them. The infant's mother may not have understood that if there was a 10% chance of the infant being neurologically normal if he survived and only a 10% chance that he would survive, then there was only one chance in one hundred of his being normal if life support were continued.

One way to assess what the family understands about the information being presented is to ask them to repeat it back in their own words. At the end of the initial family conference and at the end of each subsequent conference, the family could be asked to say what they understand the infant's condition to be. That way, misunderstandings would immediately be spotted, and could be corrected by repeating the relevant information in a way that is understood by the family—as shown by their ability to repeat the correct information in their own words. Although misunderstanding the facts seems like a trivial reason for end-of-life conflicts, it is the most common reason (4). It is also the most avoidable. Discussion of whether to limit or discontinue life support should never occur until it is clear to the physician that the family understands the prognosis. This may require repeated, calm explanations. These explanations can be accompanied by expressions of sorrow by the team members that nothing more can be done to improve things for their infant, so the family understands that everyone participating in his care wishes he could survive, and that he could be normal. In other words, that everyone has the same wishes for the infant. It is not useful to discuss limitation of life support until the family fully understands and accepts the prognosis.

They believed that God performs miracles, and a great many members of their church were praying for their infant to survive and be normal. They felt that if they agreed to limit or stop life support, members of their church would see them as lacking faith in God's ability to heal.

Here, the family fully understands that the physician is giving them a bleak prognosis, but they believe that God can intervene and heal their infant. It isn't clear how prevalent this view is, but it certainly is not rare or limited to a geographic area or a single religious or ethnic group. Situations in which a family's religious beliefs have led to conflict with clinical recommendations near the end of life have been recognized and evaluated in several recent articles (5–7). It is beyond the scope of this article to discuss different interpretations of religious doctrine.

Discussion and evaluation of the clinical facts and what is right for the patient may, at times, be enough to lead the family to change their view. One approach that has often been successful in our NICU is to ask the family to invite their own minister or a hospital chaplain of the same faith to participate in discussions about prognosis and options for treatment. When the minister understands that the infant is suffering and will almost certainly die, he/she may counsel the family that a reasonable option is to substitute comfort care for intensive care as a way of showing compassion and love for their child. Some people have idiosyncratic ideas about the teachings of their church and don't realize that their religion considers it acceptable to discontinue life support in cases of medical futility. If their minister, rabbi, priest, or imam is present during discussions, he may help them to consider such an approach. Also, within a religious framework, the parents may come to see that discontinuing life support isn't incompatible with continuing to pray for a miracle. Whatever happens once life support is stopped, the Deity they worship would still determine the outcome. We have seen families who state that this view changed their approach and who discontinued life support when, over time, they came to appreciate their infant's suffering. However, if theirs is a deeply held belief and supported by their culture, it is quite likely that they will not modify their belief, and that efforts to convince them to do so will fail. The physician and medical team may disagree with them, but understand that it is important to avoid conflict or antagonism which will only interfere with their ability to support the family and will also decrease the chance that the family may reconsider their view in time.

They knew of similar cases in which the doctors' predictions were wrong. Also they suspected that their infant might not be receiving the best possible care, because they were poor and on Medicaid.

In this case the family mistrusts the physician.

They speak of similar cases in which the doctors' prognoses were wrong, even though the clinical situations may not have been similar to the current one. Some people question whether their infant is getting the best care, because they are poor or feel disenfranchised by society. They believe that they need to fight to get their infant the same care that a more influential person's infant would receive. Many published studies show, in fact, that minorities and Medicaid patients do get less adequate treatment than patients with the same medical condition who have private health insurance (8–10). Some evidence suggests that African-American patients are less likely to agree with a physician's recommendation to discontinue ventilator support for their infant (8, 10, 11). Mistrust by African-Americans may also be a consequence of injustices in well-known clinical studies, such as the Tuskegee syphilis study, as well as disparities in health care and health outcomes. Where trust is an issue, the proper approach is to work to gain that trust. Explanations of treatment goals, efforts taken to achieve them, and why they are unsuccessful, repeated over time, are most likely to succeed. It may also help if the doctors offers to get a second opinion. In any case, understanding the family's reasons for not agreeing to stop life support will help the physician to understand why attempts to pressure them will fail.

The mother saw survival of her infant as the only solution to a life crisis. One such mother had been depressed, and her boyfriend was the only person she felt close to. She believed he would remain with her if their son survived, but would leave her if he died.

Decisions made on behalf of an infant should focus on what course of action is best for the infant. Although it is likely, and sometimes even appropriate, that parents also take into account the consequences of their decisions on other family members and even on themselves, the reason given here to continue life support is inappropriate, albeit understandable. The mother's interest is focused on what is best for her, and the infant's life is literally held hostage for the mother's gain. One can properly question whether the mother is a competent decision maker on behalf of her child, and in extreme situations it may be appropriate to ask the court to assign another guardian for the infant.

Knowing what the issue is for the mother, however, it is clear why pressure exerted on her to discontinue the infant's life support will be met with tremendous resistance. The hope is that, over time, the infant's mother and her family can be helped to focus on what the infant is going through, what his or her future will be like, and what the best decision would be. Psychological counseling could be offered, but may not be accepted or successful, since the young woman is facing several simultaneous life crises: the birth and impending death of her first child and the potential loss of her boyfriend, the most significant person in her life. The mother's parents or closest relatives or friends may be included in family conferences to support her during the crisis.

The likelihood of the infant having moderate-to-severe disabilities was not important to them. They believed that the life of every child, even one with severe or profound disabilities, had great value and should be saved. They were prepared to commit themselves to raising him if he survived, regardless of his limitations.

It is clear that people differ in how they view survival with severe disabilities. Some place great importance on intellectual functioning and would not, themselves, choose to survive an illness that left them with severe mental impairment and as a burden on their families. Others see the world differently. When a family cherishes a child with severe or profound disability and is prepared to sacrifice other life goals to provide loving care for that child, their view deserves great respect. The likelihood of success with the child will depend upon the goal of therapy. For if a family only views fairly intact, "normal" survival as acceptable and all other outcomes as negative, then there is only a 1% chance of a good outcome in the case described. But if the family will be happy to take home an infant even with severe or profound disability, then there is a 10% chance of success. Given that probability, it is understandable that they might ask that life-supporting care be continued.

Once the rationale behind the family's request to continue life support is understood and it is established that they truly understand what lifelong problems the infant will probably face if he survives, it may be less appropriate to try to change their minds. We should support their choice even if we would not choose the same course for our own infant. It is very important that all members of the medical team understand that people do have differing values, and that our role is to support all families whose values are reasonable and motivated by concern for their infant. The question isn't whether we would make the same choice, but whether the choice the family makes is a reasonable and acceptable one, given that ours is a diverse and tolerant society.

In each of the scenarios, I have tried to show that good communication can help prevent conflicts. Only by knowing what the family really understands, and what their fears, values, and beliefs are, can the physician collaborate with them in making the best decisions for the ongoing care, or end-of-life care, for their infant. In the case presented, a recommendation was made to discontinue life support because the infant had a very poor prognosis—before the physician knew what the family really understood about the infant's condition (or had much insight into their beliefs, fears, and values). They didn't accept the physician's recommendation, and this soon led to conflict about the best course of treatment for the infant. Taking time to understand the family's views first might well have avoided conflict. Not only does conflict usually fail to resolve the question of what is best for the infant, but it denies the family struggling to cope with a crisis much needed comfort and support from the medical team.

Conflicts between physicians and families concerning decisions to limit treatment for adult patients in intensive care units have been fully analyzed according to whether the conflicts originated with family, physician, or organizational and social factors (3). Presumably the same factors would exist when conflicts arise in the NICU. In what follows I discuss two factors, which I believe are barriers to optimal communication by physicians: inadequate training in end-of-life communication and time constraints.

Inadequate Training in End-of-Life Communication

Medical school curricula usually cover topics relating to death and dying (see Table 2, for instance), but rarely include practical training in the skills needed to effectively communicate with families about these issues, including how to help families deal with decisions about whether to limit or stop life support (12). Usually, physicians learn how to do this "on the job." Believing that many physicians would benefit from improved communication skills in this difficult area, the American Medical Association and several other professional societies recently published educational materials for physicians about end-of-life communication with families; but it isn't known how widely used, or useful, these written materials are (13). Physician comfort and skill levels in dealing with families about end-of-life issues vary considerably. For many, discussion of whether to discontinue life support is very difficult, and sometimes even painful. The physician is forced to deal with his or her "failure" to save the infant and thoughts about personal mortality and severe disability, and to communicate effectively with a family who may hold very different values from his or her own. The family that the physician is trying to help may also question aspects of the obstetrical or neonatal care their infant received, and as they confront the fact that their infant may die or be severely impaired, they may be in any of the stages of loss: denial, grief, withdrawal, or anger.

TABLE 2

A Checklist for Communicating Bad News

Prepare your facts.
Be sure all health care team members agree.
Invite the family to bring a few close relatives, friends, or clergy.
Include a few team members who know the patient: nurse, social worker, and chaplain.
Meet in a quiet, confidential setting.
Have all patients sit down and introduce themselves.
If the news is bad, start out by saying "I'm (we're) so sorry to have to tell you…"
Review patient's condition and treatment up to the present time.
Keep your message straightforward. Avoid medical jargon.
Discuss all realistic options.
Don't discuss alternatives that won't work.
Discuss measures that can be used to minimize pain and discomfort.
Don't discuss limiting life support until it is clear that the family fully understands and accepts the reality of the situation, usually at a subsequent meeting.
Always ask the family to explain the patient's situation in their own words.
Arrange for the next meeting time, place, and attendees.

Time Constraints

A second major barrier is time constraints. It takes considerable time to establish a meaningful relationship and get to understand a family's level of understanding, fears, beliefs and values. Yet this is usually attempted during a series of fairly brief meetings with the family. The pressures to increase productivity, to care for more and sicker patients, and to shorten hospital stays makes it even more difficult to achieve the necessary level of communication. In academic medical centers, additional demands exist to teach and do research. Nonetheless, meaningful communication with families is so crucial for making the right decisions for their infant and to support the family, that adequate time for it must be found.

If time is scarce for the attending, it is even scarcer for the residents. Traditionally, residents have been responsible for much of the communication with the families of the patients assigned to them. But this has become more difficult in recent years. Not only do residents now have to take care of sicker infants and deal with shorter lengths of stay, they are also required to work fewer hours. Because attending and work rounds are done in the morning, most family conferences are scheduled in the afternoon. In the past, residents were available to participate in these conferences on most afternoons, but now they are unavailable if they worked the previous night or if they are assigned to an afternoon continuity clinic. Consequently they miss many learning opportunities during family conferences that the attending physician holds with patients' families. This will greatly decrease their opportunity to communicate with "their" families and learn the important skills involved. We need to find new ways to improve resident communication skills within the constraints of the work-hour guidelines.

Conclusion

Recently there has been understandable concern about how to proceed when families make apparently "inappropriate demands" to continue life support, resulting in needless suffering by the patient and a waste of scarce and costly medical resources. This problem arises with sufficient frequency that one state, Texas, recently passed legislation that provides an extrajudicial due-process mechanism for resolving end-of-life conflicts (14). The process begins with formal committee review of the medical appropriateness of continued care, and if the care is found to be inappropriate, transfer of the patient to another hospital is the only alternative to discontinuation of that life-prolonging therapy. The legislation exempts both the physicians and hospital from civil or criminal liability if they discontinue care after diligently following the appropriate procedures. Although this sort of approach may be needed in rare situations, it is always far better, when possible, to avoid such end-of-life conflict.

I propose that such conflicts can be prevented in many or most situations if physicians become better at communicating with families about end-of-life issues (6). How can they accomplish this? For one thing, communication and understanding can be improved if a palliative care professional such as a nurse, nurse practitioner or social worker who has developed the necessary skills and has more time available, works along with the physician to communicate with and support the family. Time constraints that have always existed in medical practice are more acute today. But adequate time must be found to understand a family's personal experience, reasoning, feelings, and religious and ethical beliefs, in order to be able to support them and to help them make the best possible decisions for their critically ill infant. Doing so can also prevent end-of-life conflicts. While this discussion focuses on end-of-life decision making in the NICU, it is equally appropriate for preventing end-of-life conflicts that may arise throughout the hospital.

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When Parents Request Seemingly Futile Treatment for Their Children

John Lantos, M.D.

Abstract

This paper reviews the development of the concept of medical futility, particularly as it applies to pediatrics. It discusses the difference between technical considerations and value considerations in futility determinations, and then breaks down the concept of futility into four components—power, money, trust and hope.

Key Words: Futility, doctor-patient relationship, power, economics, trust.

The topic of medical futility is difficult to address concisely. So much has been written about it over the past decade that it has become complex, arcane, and stale all at the same time. Furthermore, as a practical matter, as opposed to a theoretical one, I think it is virtually a non-issue in pediatrics today. That is because, as a practical and legal matter, the controversy has been essentially resolved. There are virtually no situations in which courts will give permission to doctors to withhold or withdraw treatment that parents request. Instead, courts have allowed parents to demand intubation of anencephalic babies and continued home ventilation of brain-dead children. Courts will, on occasion, forgive doctors who withhold or withdraw therapies over parental objections, but, in order to get that forgiveness, doctors need to take the risk that punishment, rather than forgiveness, may come their way. Most doctors are not willing to do that or, if they are, soon come to realize that they must overcome not just parents but their own legal counsel as well.

Conversely, courts rarely allow parents to opt for treatment withdrawal if doctors think treatment is indicated. So it appears that the current working policy in the US is that there must be consensus among doctors and parents in order to stop treatment, and that disagreement always leads to continued treatment. It is interesting to speculate about how things got this way. My own explorations of the futility issue over the years, which include inconsistencies, twists and turns, mirror the national debate so, to review the national debate, I will review some of my own past speculations on the issue.

I first started thinking about futility after the Baby Doe controversy in the mid-1980s (1). I was a fellow in clinical medical ethics at the University of Chicago, and was puzzling over the explanatory guidelines that were published after Congress passed amendments to the Child Abuse and Treatment Act (1). These guidelines incorporated within them the moral outrage that followed the death of a baby with Down syndrome because his parents refused to consent to surgery for an easily correctable esophageal anomaly. The goal of these guidelines was to limit the situations in which such parental refusals had to be complied with. In other words, they addressed situations that were the opposite of the typical "futility" controversies. (Today, we are talking about situations in which parents want something done that doctors think is futile. In that situation, the doctors desperately wanted to treat the baby and even sought a court order to do so, but the parents did not want treatment.)

The guidelines may have been the first to incorporate within them the concept of medical futility. Interestingly, they didn't use it as it has come to be used since then—to define situations in which doctors are justified in not providing treatment (or, according to some formulations, obligated not to provide the treatment.) Instead, they used it to define situations in which it was permissible for parents to refuse treatment without being judged neglectful. Those were situations in which the treatment was either "futile" or, in the memorable words of the guidelines, "virtually futile and inhumane." None of these three concepts—futile, virtually futile, or inhumane—was defined.

This definitional ambiguity in guidelines that were meant to resolve ambiguity led me to take up two projects. The first was an empirical study. Working at The University of Chicago with neonatologist Bill Meadow, I started with the intuition that cardiopulmonary resuscitation (CPR) might be futile for certain very sick premature babies. The intuition was based upon our understanding that CPR was often provided to such babies for multisystem organ failure—and the recognition that CPR had not been designed for this sort of problem or for this patient population. We studied outcomes after CPR was given to those babies and found that for a

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subset, namely those babies who received CPR outside the delivery room—that is, after the first minutes of life, when many had a transitory cardiac or respiratory depression—and within the first three days of life, none of the 39 babies survived (2). Our statistical analysis showed that, because of our small sample size, the confidence interval on our 0% survival rate went up to 7%. That is, the most we could scientifically claim was that the survival rate was likely to be very low, but we couldn't say with statistical certainty that it was zero. We also showed that, given the nature of statistics and confidence intervals, it would be difficult to ever do a study large enough to get the confidence interval small enough to prove that a particular treatment was absolutely futile. Instead, we raised the question of whether this sort of finding might satisfy the Baby Doe criteria, i.e., that the treatment could be considered "futile." This would mean that it was one that parents might be legally permitted to refuse.

At the same time, we started a completely different sort of inquiry into the nature of medical futility. Working with the fellows and faculty of The University of Chicago's MacLean Center for Clinical Medical Ethics, we conducted an historical inquiry into the concept of medical futility and a theoretical analysis of the content of the concept (3). Interestingly, at that time, a search of Medline, the National Library of Medicine's database, turned up no articles that used the concept of futility in its modern context. That is, there were no papers published between 1966 and 1984 that discussed the ethical implications of futile medical treatments. It seemed to be a non-issue. There were several ancient discussions: Hippocrates, for example, warns physicians not to treat patients who have been "overmastered by their disease"; Jewish tradition considers how the moral obligations of patients to preserve their own lives (and loved ones and physicians to help them) shifts when death is imminent; and the traditional Catholic distinction between ordinary and extraordinary treatments may have an element of futility implicit within it. But doctors in the 1960s and 1970s didn't seem to worry much about futility. The only hits we had in Medline using "futility" as a keyword were for the psychiatric literature and articles discussing feelings of futility as a component of some depressive syndromes. So we thought we were the only ones thinking about it. (How wrong we were!)

Our paper (3) argued that there were two components to any futility determination. First, someone must determine the goals of treatment. If, for example, the goal of insulin therapy is to cure diabetes, then the therapy is futile. It can only control the disease, not cure it. If, however, the goal is to prevent hyperglycemia, insulin is quite effective. If the goal is to prevent the long-term complications of diabetes, then insulin is only partially effective. For CPR, a similar sort of analysis might start with several possible goals. CPR could be intended to provide temporary oxygenation and circulation, to restore a spontaneous heart rate, or to lead to a full cardiovascular and neurological recovery from a cardiac arrest. CPR cannot be said to be "effective" or "futile" until its goals are defined. Once the goals are defined, there is a second element of any assessment of futility: the likelihood that the treatment will succeed in reaching those goals. The first component, we argued, properly belonged to the patient, not the doctor. The second component was the proper domain of the doctor, or, more accurately, the medical profession and its health services researchers, clinical epidemiologists, and statisticians. The first component was more value oriented, the second more quantitative. Both incorporated significant uncertainties. We suggested that both must be considered in any determination of futility.

In the meantime, the field of futility studies took off. Over the next ten years, hundreds of articles and numerous books appeared about medical futility. Hospitals developed and tried to implement futility policies. There were numerous court cases testing the limits of doctors' authority to make unilateral determinations of medical futility, thus overriding patients' or their surrogates' demands for continued treatment. All this sudden attention seemed curious to me. Why is it that nobody seemed to care about medical futility until 1985, and then suddenly it was the hottest issue in medical ethics? The answer seemed to be tied in with both the scientific and the political developments of the time. Scientifically, we were just starting to understand the implications of some of the technologies that had been developed over the previous decades. For example, renal dialysis first became widely used in the 1960s, long-term mechanical ventilation did not become practically effective until the 1970s, and solid organ transplantation was really a technology of the 1970s. The 1980s saw the first trials of an artificial heart. By the 1980s, people were starting to realize just how complicated were the decisions arising from these "half-way" technologies, these treatments that could sustain biological or physiological life but might not lead to improvement or cure. At the same time, the political environment was changing. Concern about expanding access had dominated health policy in the sixties. By the eighties, cost containment was the primary political concern, and Congress enacted a new payment method for Medicare.

I started working with a colleague, neurologist Bob Taylor, who was then a fellow at The MacLean Center, on a paper in which we argued that there was a fundamental economic element to futility determinations (4). This economic element became salient after the implementation of diagnostic-related groups (DRGs), when the financial incentives for doctors and hospitals shifted from rewarding excessive treatment toward rewarding the limitation of treatment. The shift was from a reimbursement system based upon doctors' charges—whatever doctors and hospitals charged is what they got paid—to a reimbursement system based on calculations of what the average cost of treatment for any particular diagnosis ought to be. Under a prospective payment system, hospitals received a set fee for the treatment of, say, a myocardial infarction, septic shock, or a motor vehicle accident victim with head trauma. Clearly, under this new system, it was in the interest of doctors and hospitals to limit treatment and get patients out of the hospital quickly and efficiently; and this, we argued, was the underlying stimulus that led doctors to rediscover the ancient concept of medical futility. We concluded that futility cases were really about money, and that they quickly came to be about power and trust.

My final try at an analysis of the issues found in futility controversies was an attempt to assess the whole topic in the late 1990s, after ten years had passed. Working with Mark Siegler and oncologist Paul Helft, I reviewed what we called "the futility movement" (5). We characterized that movement as an attempt to change public policy and local hospital policy in order to empower doctors to override patients' requests, or demands, for treatments that the doctors thought were futile. We argued that most futility policies that tried to thus empower doctors were, essentially, bluffs. The policies were written in such a way as to acknowledge that, if disagreements persisted, the cases would ultimately have to be resolved by courts. And we showed how reluctant most judges were ever to permit such prospective futility determinations by doctors to override the wishes of patients and family members. Many such cases had reached the courts. In such cases, different courts used all sorts of reasoning but generally came up with similar answers—that patients' or families' demands would override doctors' refusals. The only exceptions were the cases that reached the courts after a doctor had already imposed a futility determination, the patient did die, and the family then sued. In those cases, the courts generally did not hold the doctors liable. In short, courts seemed unwilling to give permission for prospective futility determinations but somewhat willing, on occasion, to offer forgiveness to doctors who made such determinations.

Why did it come out this way? Well, partly because of the issues that we raised in that early paper, where we broke futility up into its components—the goals of treatment and the likelihood of success. The courts were reluctant to cede authority for the first to doctors and were, it seems, not particularly willing to ignore the confidence intervals, the rare chances of success in even the most unlikely situations. Put another way, they seemed to recognize that unilateral futility determinations were usually either one of two things. One, they could be masked quality-of-life determinations. For example, when doctors say that mechanical ventilation for a patient in a persistent vegetative state is futile, they don't really mean that mechanical ventilation will not sustain the patient's life. Instead, they fear that it will work—it will sustain biologic life but life of a quality that they deem insufficient to warrant the effort. To the extent that futility determinations are, in essence, such quality-of-life assessments, they should be identified as such and dealt with as such.

Alternatively, futility determinations can be probabilistic assessments that success is extremely unlikely. But in such situations, the only downside to trying a treatment that is unlikely to work is economic. It will be a wasted expenditure. To the extent that this is the case, futility determinations collapse into rationing decisions.

So the domain of true futility—that is, situations that are neither disguised quality-of-life assessments nor disguised rationing decisions—is extremely small, perhaps non-existent.

All this is not to say that the concept of medical futility is not a useful or important one. It is important, there are situations in which treatment is futile, and they can often be identified prospectively. Generally, in such situations, doctors explain this to the patients or their surrogates, the latter understand and accept the situation, and treatment is withheld or withdrawn. The concept of futility, in those cases, has a moral role in helping absolve patients or surrogates of the moral obligation to continue treatment. Futility has not, however, been as useful as a moral trump card to resolve intractable disagreements. Instead, it is, as it should be, a concept to be used judiciously and with trepidation, to help patients or family members identify and shift their perception of their own moral obligations.

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When Staff and Parents Disagree:

Decision Making for a Baby with Trisomy 13

Linda B. Siegel, M.D.

Abstract

Parents often make medical decisions for their children. As pediatricians, we must be sure that the decisions are medically informed. At times, we may disagree with the decisions that parents make and must decide if they are acting in the best interest of their child. This article presents a case in which these issues arose regarding a child with trisomy 13.

Key Words: Ethics, child, trisomy 13, medical futility.

Case

Michael, a 4-month-old baby with trisomy 13, was admitted to the pediatric intensive care unit (PICU) for respiratory distress. He had been born to a 22-year-old mother and a father in his 20s. The parents were married and this was a planned first pregnancy, with good prenatal care. The pregnancy was uncomplicated and the baby was born at term. At birth he was noted to be dysmorphic and small for his gestational age and was admitted to the neonatal intensive care unit (NICU). He was diagnosed with trisomy 13 at 6 days of age. He had ventricular septal and atrial septal defects, right micro-ophthalmia, right-sided choanal atresia, hydronephrosis, undescended testes and microcephaly. He was in the NICU for 3 months, and due to his fragile state and ongoing medical needs, was then discharged to a chronic care facility.

Trisomy 13, which occurs in approximately one in five thousand live births, presents with many associated congenital anomalies. These anomalies include heart defects, brain defects, breathing problems, seizures, severe mental retardation and deafness. About 50% of patients with trisomy 13 will die within the first month of life, and only 5–10% will survive for more than one year.

Michael's parents were deeply involved in his care. The father worked and the mother was planning on staying home with the baby. They were Jewish, with strong faith and beliefs based on that faith, and good family support. They also relied a great deal on a rabbi to help them make important decisions.

When Michael was readmitted to the hospital, not long after his initial discharge, it soon became obvious that some of his respiratory problems were related to aspiration of his feeds. He had a barium swallow to confirm the aspiration and was then started on nasogastric (NG) tube feeding. The aspiration appeared to be related to his underlying neurologic impairment, and we thought that Michael would never be able to eat by mouth again. Despite the NG tube feeds, his respiratory status deteriorated to the point where he required intubation. The parents were consulted, and they elected to have Michael intubated despite his poor long-term prognosis. Michael had a difficult time while intubated, and required sedation and paralysis to maintain his oxygen levels. He had frequent life-threatening episodes despite being on a ventilator. Six days after intubation, he was diagnosed with a seizure disorder and was started on medication. It soon became clear that Michael would not be able to come off the ventilator quickly, and discussions about long-term plans were held with the family.

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The medical team, together with the social worker, spoke with Michael's parents at length about Michael's long-term prognosis and the options for further care. During the conversations, the father was the one who asked and answered questions, while the mother was mostly quiet. They were young, but intelligent, and obviously concerned about their son. They were also medically "savvy" after Michael's long NICU stay and had educated themselves about his condition. We discussed Michael's poor prognosis for neurologic function, as well as the likelihood of a very early death. Michael's parents were quite aware of the life expectancy and neurologic prognosis for children with trisomy 13. We talked about quality of life versus quantity of life. The options presented to the parents included withdrawal of support with palliative care, or a tracheostomy and at least short-term ventilator support. We did not feel that Michael would survive a trial of extubation, and withdrawal of support was not an option for the parents. Obviously, long-term intubation, which would require acute care hospitalization, was also not an option.

Ultimately the parents elected to have a tracheostomy placed for airway protection and ventilator support, and a gastrostomy tube placed for feeding. Michael had a somewhat difficult postoperative course, but eventually was able to be discharged on a ventilator to a different chronic care facility, with the hope that he would eventually be able to go home.

Discussion

Michael's case was difficult for the medical staff in several ways. We saw a baby with a very poor long-term prognosis, who we felt was suffering significantly. He often appeared uncomfortable, especially with suctioning and other medical interventions. At the same time, he did not appear to get any pleasure from life. He did not smile and did not seem to recognize his family. His prognosis for neurologic function was extremely poor. The parents were involved and concerned, but not at the bedside for extended periods of time, so they did not see the suffering that we saw throughout the day. For the medical team, the burdens of treatment seemed greater than the perceived benefits.

In addition to those concerns, there was a sense that the father was making the decisions and not including the mother. The ultimate goal for the father was to take Michael home, a plan with which the mother did not seem quite comfortable.

Although Michael's long-term prognosis was poor, we could not say for certain that he would die within the next few months, which made it more difficult to argue for limitation of care. The parents had educated themselves about trisomy 13 and understood the poor prognosis, but at the same time they had read on the Internet about children who had survived with the condition for more than a year. For obvious reasons, they were holding onto that image very closely. While we were able to have frank discussions with them about Michael's future, they remained firm in their hopes for him.

As medical professionals, we see many neurologically impaired, chronically ill children who suffer through recurrent hospitalizations and medical interventions, only to die a premature death. So while treating Michael may not have been absolutely futile, it seemed that way for many on the medical team. As pediatricians, we must constantly balance the prognosis, needs and well-being of the child with the hopes, wishes and needs of the parents.

Ultimately, we agreed to what the family wanted, and were comforted by the fact that they were making an educated choice and a decision that they felt was in their child's best interest. In the end, the parents will carry the weight of their decision with them forever. When the benefits of treating or withholding treatment are uncertain, we should respect the family's informed decision.

An Exploration of the Ethical, Legal and Developmental Issues in the Care of an Adolescent Patient

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Abstract

Providers of health care to adolescent patients face numerous challenges. In addition to increased risk for many health problems, adolescent patients may bring complex ethical, legal and developmental questions to bear as they seek medical services. This article describes the case of one such adolescent patient and discusses some of the attendant issues faced by her physician. For example, providing reproductive health care to teenage patients without the knowledge of parents or guardians requires familiarity on the part of providers with relevant state and federal law. Additionally, providers must be aware of financial barriers and they need to acquaint themselves with available services such as New York State's Family Planning Benefit Program. Attention to their patients' stages of cognitive and emotional development should inform providers' advice to adolescents, and an understanding of the importance that supportive adult relationships play during adolescence is essential to fostering healthy development. Open communication between adolescent patients and their parents or guardians should be encouraged, while maintaining the primary obligation of providing confidential care.

Key Words: Adolescent health, confidentiality, health insurance, cognitive development, ethics.

Care of the adolescent patient involves various challenges for the clinician. In addition to knowing the common physical complaints and problems of teenagers, an understanding of the cognitive, emotional and psychosocial development that occurs during adolescence is essential for successful treatment and management of teenage patients. The adolescent patient poses not only a unique set of diagnostic possibilities to the clinician, but also distinct ethical and legal considerations. This article details a recent case involving an adolescent and explores some of the ethical and legal issues faced by the patient's physician. Though each adolescent patient brings his or her own unique challenges to those who provide medical care, this article addresses some of the difficulties providers may experience on a regular basis when caring for this population. An understanding of the extent and limitations of confidentiality is of particular importance for patients, their families and medical providers. Moreover, it is imperative that providers strive to gain the trust of their adolescent patients, and to facilitate communication between patients and their parents or guardians.

Case

Jessica is a 15-year-old girl who has been a patient of the same pediatrician in New York City since the age of five. She comes in with her mother for a routine check-up. After asking her mother to step out of the room, the physician asks Jessica about sexual activity. Jessica confides that she is having consensual sex with her 17-year-old boyfriend. She has been using condoms intermittently, and has read about the contraceptive patch on the Internet. Jessica tells the doctor that her mother does not know that she is having sex, and would "kill her" if she found out. Jessica wants to have a prescription for the patch, but doesn't know how she will be able to afford it. Although she has private insurance through her family, she is worried that her parents will find out about the prescription if she uses the insurance to cover the cost. As her physician discusses the options available to her, Jessica also expresses concern about possible

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exposure to HIV and asks to be tested. However, she is concerned that the results would need to be shared with her mother if the test were to show that she is infected with HIV.

The Issue of Confidentiality

There are several issues that present themselves in Jessica's case. The primary concern for Jessica is that her mother not discover that she is sexually active. Disclosure of her history of sexual activity would have a significantly negative outcome, and thus Jessica is unwilling to share this information with her mother. However, she is a minor and seeks a prescription. Who has the right to consent for care in this case?

In general, parents or guardians have the right to give informed consent for the medical care of their minor children. However, there are circumstances in which exceptions to this rule apply.

The first exception applies to emancipated minors. "Emancipation" has been defined as the renunciation of parental right to a child (1–3). A minor is considered emancipated if one of the following events has occurred: he or she is married; he or she is in the armed services; he or she has established a home and is financially independent; or his or her parent has failed to fulfill parental support obligations and the minor seeks emancipation. In general, emancipated minors can consent to their own health care (4). According to the New York Civil Liberties Union, the few New York courts that have addressed this issue have all consistently decided in favor of allowing emancipated minors to give consent (1).

The second exception is based on the mature minor doctrine, which has been established by legal precedent in many states. A minor may consent to medical care and treatment without parental consent if the physician determines that the minor has the maturity to make independent decisions. In New York, a mature minor is a minor who is emotionally and intellectually mature enough to give informed consent and who lives under the supervision of his parent or guardian (1). The mature minor doctrine usually applies whenever no other exceptions to parental consent apply, and parental involvement is impractical or problematic, or may discourage the adolescent from seeking needed medical care (5).

The third exception is based on the category of care the minor is seeking. In the State of New York, a minor who understands the risks and benefits of proposed and alternative treatments may generally make health care decisions without parental consent for reproductive health care, including family planning, abortion, pregnancy-related care including prenatal care, care during labor and delivery, and care for sexually transmitted infections (STIs) (4). Confidential "comprehensive voluntary family planning services" are available via federal Title X funding to "all persons desiring such services," including "a special emphasis on preventing unwanted pregnancies among sexually active adolescents," with no stipulated age requirement (6). In addition, minors who can give informed consent can obtain confidential services regarding STI screening and treatment, and New York State law forbids the release of medical information to parents without the patient's permission (7). Thus, Jessica has the right to consent to confidential reproductive health services.

Because Jessica has expressed interest in HIV testing, she should be given the option of having either an anonymous test at a Department of Health site or a confidential test at her physician's office. In an anonymous test the patient's name is not revealed; informed consent and test results are tracked with a coded system that has no linkage to the patient's identity. Should Jessica decide to get confidential testing during her office visit, she must understand that her test results can be subject to reporting and contact notification. In particular, her physician must inform Jessica that if her HIV test result were positive, her name would be released to the Department of Health, as would the names of her known sexual contacts (8, 9). However, she would not be required to give contact information for her sexual contacts (such as her boyfriend), and she would not be denied treatment or be criminally prosecuted based on failure to disclose (10). In addition, even though Jessica can consent to her own HIV testing, she must also be made aware that her results could be shared with her mother if her physician deems that she lacks sufficient maturity to consent for the necessary follow-up care (11, 12). She should also be reassured that such disclosure would only occur if the physician considered it medically necessary, and Jessica would be allowed a sufficient amount of time to disclose on her own.

Payment for Confidential Services

As a resident of New York State, Jessica has the right to consent to reproductive health care without parental notification. However, this case illustrates another difficult issue that may arise when caring for adolescent patients. The financial burden entailed in obtaining truly confidential health care is of paramount concern, as many adolescent patients lack funds to pay for care independent of their parents or guardians. Unfortunately, involuntary disclosure can occur through billing or insurance records. This possibility of disclosure, whether actual or perceived, is one of the major barriers to accessing care among teenagers (13). Adolescents often express fear that any insurance or billing correspondence will prompt questions from parents or guardians. Most insurance companies require that the physician disclose the treatment offered as a stipulation for payment. This information is listed in the "explanation of benefits" statement (or EOB) that is mailed to the patient's home and often read by the patient's parents, even when addressed to the patient (14). Because parental disapproval of their children's sexual activity can, in some cases, manifest as verbal or even physical abuse, or in forcing the child to find another place to live, the negative impact of such breaches of confidentiality on patients' quality of life can be considerable.

This discrepancy between an adolescent's right to confidential care and the reality of lack of access because of insurance coverage has led New York to create a public health insurance program to help guard minors' confidentiality: the Family Planning Benefit Program (FPBP). Through FPBP, adolescents may apply for limited Medicaid coverage for family planning services without parental involvement in the application process. Teenagers are considered for eligibility without regard to parental income or insurance status, and family planning services will be billed to FPBP rather than to the patient's private insurance. EOBs are not sent to the patient, so that adolescents can receive services and providers can seek payment without worrying about breaches in confidentiality.

In New York State, FPBP offers a mechanism by which a significant barrier to confidential care can be overcome. Similar programs are available to adolescents in California (15). However, payment for confidential care may be a barrier to adolescents in other states. Federal funding for nationwide family planning services is available in the form of Title X grants; however, these funds may not be used for patients seeking abortion. Also, the ability of adolescents to obtain confidential care has been threatened by proposed legislation that would require parental consent for minors seeking treatment at a Title X-funded facility, but thus far such measures have been unsuccessful (16). An awareness of available resources is of particular importance to providers of care to adolescents, as this awareness may be the only means by which their patients can access appropriate confidential care.

Cognitive Development

By law, Jessica has the right to provide consent for her own reproductive health care and be enrolled in insurance programs to cover the cost of the treatment she chooses. From a legal perspective, she need never inform her mother of her decision at all. However, there are other issues for her health care provider to weigh when giving her not only medical care, but advice.

Adolescence is a time of rapid and often disorienting change for young people. Piaget has described the process of cognitive development at this age as a "liberation from the concrete in favor of interest oriented toward the non-present and the future" (17). Thus, the ability to connect their behaviors with current or future adverse outcomes is still developing in teenagers. However, preventable behavior is responsible for over half of adolescent morbidity and mortality (18). This reality is often well understood by parents or guardians, and the conflict between the patients' preferences and the teenager's own wishes may be significant. It is often left to the health care provider to mediate in these situations and find a mutually acceptable compromise.

During the transition from childhood to adolescence, a teenager's primary influences shift. Parents are often eclipsed by peers during early adolescence, and as development continues the patient eventually begins to make decisions based upon his or her own best judgment. This is an integral step in the achievement of "identity," which is the goal of late adolescence, according to Erikson (19). Young adults who perceive themselves to be primarily responsible for their own health, or have an internalized "health locus of control," are more likely to engage in healthy behaviors (20), and it is important to foster this emerging sense of autonomy. However, it is equally important for the physician to understand that Jessica may require more external guidance at this point in her psychosocial development.

Whenever possible, adolescents should be encouraged to communicate with their parents or guardians. Jessica's relationship with her mother should be fully explored by her physician. It is likely that Jessica anticipates a far worse reaction from her mother than would actually occur. Further, the physician should offer to facilitate the conversation between the two of them in the neutral setting of the health care environment. Should Jessica adamantly refuse to involve her mother in her family planning decisions, she and her physician should find another trusted adult in whom she could confide. And the importance of supportive adult relationships should be emphasized in the follow-up visits.

A clear discussion about confidential care, between providers, patients and their families, is an essential part of anticipatory guidance as adolescence approaches. In addition to facilitating parents' understanding of their child's evolving health care needs, this discussion can diminish future conflict between a parent who wishes to be fully informed and a teenager who needs and wants to obtain confidential care. Furthermore, it may provide a backdrop for encouraging young patients to discuss their health care decisions with their parents as they grow older.

Summary

Jessica's case highlights many common ethical and legal challenges that providers face when caring for adolescent patients. Adolescence is a time of testing boundaries and expanding one's sense of autonomy. However, the ability to make well-considered decisions is still forming, and health care providers play an integral role in supporting adolescent patients as they face the unanticipated consequences of their choices. A thorough knowledge of the legal provisions or obstacles such patients face is of utmost importance to those caring for them, as the health care provider may be the only person these vulnerable patients can turn to. Additionally, the developmental needs of these patients must be understood, and efforts to foster supportive adult relationships should be encouraged. The primary obligation that providers have to deliver care to their patients should not overshadow the benefits of open communication between adolescents and their parents, whenever possible.

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Children as Research Subjects:

Moral Disputes, Regulatory Guidance, and Recent Court Decisions

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Abstract

The millennium has ushered in a new era of oversight for pediatric research, with renewed moral and legal attention to the upper thresholds of potential harms to which children may be exposed in studies. Watershed events discussed include: First, the deaths of two research subjects, allegedly due to insufficient oversight by the investigators and their institutional review boards. Second, the courts expressed concerns about research policies for incompetent persons or children in two cases, *T.D. v. N.Y.* and *Grimes v. Kennedy Krieger Institute*, and reinforcement of the principle that the best interest standard must be used for incompetent persons even in research. Third, the Best Pharmaceutical for Children Act and the Pediatric Rule created incentives as well as uncertainty among Institutional Review Boards and researchers about conducting pediatric studies. Fourth, the Office of Human Research Protection signaled the start of more rigorous oversight with its public rebuke and suspension of a National Institute of Child Health and Human Development pediatric obesity study. Failure to clarify the meaning of the pediatric regulations has sometimes misled generally risk-averse institutions and dedicated investigators about what is permissible.

Key Words: Ethics, legal, research, pediatric, Grimes v. Kennedy Krieger Institute, OHPR, Best Interests Standard.

IN NOVEMBER 2000, the federal Office of Human Research Protection (OHRP) suspended a National Institute of Child Health and Human Development (NICHD) pediatric study on the causes of obesity, posting its concerns on the World Wide Web for all to see. The OHRP determined that aspects of this research were too risky for healthy children to be enrolled without special federal approval, and this approval had not been obtained. The OHRP required that certain actions be taken by December 8, 2000, including modifying the study and devising a plan about whether or not to contact "the parents or guardians of the subjects who participated in the…research and inform them of their child's inappropriate enrollment in this research (1)." The OHRP also asked for "a list of active research protocols being conducted by the NIH [National Institutes of Health] of intramural research program that involves normal, healthy children." The OHRP was particularly concerned about an "insulin tolerance test designed to induce hypoglycemia (a blood sugar less than 50 mg/dL) in normal children." The dangers of infusion of insulin into healthy children generated the most controversy over the study. The OHRP requested information about the "hundreds" of children that the investigators claimed had been involved in this sort of research.

Investigators in the research community were stunned by the public manner in which these researchers were notified and rebuked. They correctly concluded that a new era in oversight and compliance had begun. Consequently, Institutional Review Boards (IRBs) and pediatric investigators wanted more information and direction about how to determine the upper threshold of research risk that was permissible for children. They wanted to know when local IRBs could make decisions and when they needed special federal approval.

In what follows, I will first state the central moral problem in pediatric research policy, and offer some of the regulatory responses to it. After clarifying the current U.S. regulations governing assessment of these risk thresholds, I will turn to events occurring in the last few years, which have led to a new era of oversight for pediatric research. These include not only OHRP's suspension of an NICHD pediatric obesity study but also the Best-

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Pharmaceutical Act, the Pediatric Rule and the deaths of two research subjects. The courts also expressed concerns in *T.D. v. N.Y.* and *Grimes v. Kennedy Krieger Institute* about how well subjects were being protected and it reinforced the fact that the "best interest" standard must be used for incompetent persons, even in research. I will argue that the failure to clarify the meaning of the pediatric regulations has sometimes misled generally risk-adverse institutions and dedicated investigators about what is permissible.

The Central Moral Problem

The central moral problem in framing pediatric research is how to formulate a policy that promotes the well-being of all children by encouraging research, while at the same time protecting individual research subjects (2). Some policies protect children to such an extent that they do not allow them to be enrolled in any research whatsoever. For example, the Nuremberg Code (3) states that no research may be done without the subjects' informed, voluntary and competent consent. Such a policy obviously excludes all persons who cannot give informed, voluntary and competent consent, such as most children. The difficulty with this policy is that unless some research is done with pediatric subjects, there can be no genuine improvement in care for children. If clinicians are forced to use untested interventions, they will probably endanger their patients. On the other hand, if they use only tested interventions and research is not permitted, then they are severely limited in their treatment options (2).

The World Health Organization's Declaration of Helsinki adopted another policy before 2000 (when it radically changed its position) (2, 4). In these pre-2000 policies and revisions, the WHO stated that no research could be done using subjects who could not give informed consent unless the study had direct therapeutic benefits for the individual. This policy was an advance on the Nuremberg Code because it at least allowed testing of different therapies for children, such as different cancer or asthma treatments, if the different arms of the study were genuine therapeutic options that were being compared. Nonetheless, the Helsinki policy seemed unduly restrictive. For example, many important studies on growth and development pose virtually no risks to the subject, yet cannot be regarded as therapeutic studies when the children are not sick. Yet these studies are important in determining whether some children are thriving, since they are needed to compare their growth and development to those of a norm. It seems unreasonable to claim that one is acting in their best interest by prohibiting these low-risk, but important studies (2).

The U.S. (5), the Council for International Organizations of Medical Sciences (CIOMS) (6), and the U.K., Canada, South Africa and many other countries take a very different approach (2, 7). To determine what studies should be approved, they seek to balance potential harms and benefits. Typically, they set different levels of risk and different sets of requirements at each risk level. I will focus on the U.S. requirements. I will show that these rules are vague and allow such a wide range of interpretation that pediatric investigators dedicated to the well being of children and reasonably risk-averse institutions were caught off guard by a new era of more restrictive standards based upon these rules.

The U.S. "Balancing Act" Approach: Four Categories of Research

The U.S. regulations established four categories of research (see Table) distinguished primarily by the risk of harm and the potential benefits to the potential subjects (5). The overarching concept is that the greater the risk of harm, the greater the need to justify the benefits and importance of the study, and the greater the need to obtain rigorous consent from guardians and assent from the children, if possible.

§46.404

The first research category is for studies with only minimal risk of harm and is often known by its numbering in the U.S. Code as "404" (Table). Because the risks are so low, these studies may be conducted even if there is no direct benefit to the subjects. Such studies require the approval of the local IRB, the assent of the child if possible, and the consent of one parent. Growth and development studies and chart reviews are examples of important low-risk studies that may not directly benefit the subjects. There is considerable advantage to having a study classified under this heading, because it enables investigators to obtain expedited review, modify or waive consent, or allow vulnerable subjects or others who lack decision-making capacity to be enrolled in studies (8).

The U.S. regulations define minimal risk as meaning "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests." This definition contains

TABLE

Research Involving Children, Which DHHS Is Permitted to Fund or Conduct.

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§46.404 Research not involving greater than minimal risk.
DHHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) the risk is justified by the anticipated benefit to the subjects;
(b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
(c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure [that] is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) the risk represents a minor increase over minimal risk;
(b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
(c) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
(d) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.407 Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. DHHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

(a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
(b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
    (1) the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or
    (2) the following:
        (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
        (ii) the research will be conducted in accordance with sound ethical principles;
        (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

SOURCE: Quoted from U.S. Code of Federal Regulations (45 CFR § 46.404-407).

DHHS = Department of Health and Human Services, IRB = Institutional Review Board.

two parts, and because there is an "or," only one needs to be satisfied. The first part uses "everyday risks" as a benchmark for minimal research risk, saying that to be minimal, research risk must be like that of everyday risk. However, there needs to be a moral justification for taking "everyday risk" to be a legitimate guide for low-risk studies (7). That is, even if we know the probability and magnitude of the daily risks all of us encounter (which can include drive-by shootings, SARS, and terrorism) well enough to establish the "minimal-risk" standard for research, it is unclear why everyday risks are morally relevant or justified.

The problem with the "everyday risk" part of the definition is that it allows too high a level of risk. This may be illustrated by the NICHD obesity study. Initially, the IRB decided that this study, with its infusion of insulin into healthy children, had no more than a minimal risk because they judged that these procedures were safer than the everyday risk of playing in traffic. The minutes from this meeting state (1):

> Several members of the Committee explored the meaning of minimal risk and what a child might encounter in a visit to the doctor or while playing in traffic. It was felt that spending several hours in the Clinical Center in a clamp experiment would be safer than playing actively on sidewalks and streets.

In halting the study, the OHRP made it clear that "...this research involves greater than a minimal risk. In particular, the hyperglycemic, euglycemic, and hyperinsulinemic clamp procedures involve greater than minimal risk. Other study interventions, such as the two-day, one-night hospitalizations for intensive metabolic evaluation, may also involve greater than minimal risk for some subjects" (1).

The other part of the definition of minimal risk is more promising, since it benchmarks the analysis of "minimal risk" research to the reasonably well-understood notion of routine medical or psychological examinations or tests. I have argued in detail elsewhere that we should drop the "everyday risk" standard and simply understand minimal risk as no more than the sort of risks we all encounter in routine medical or psychological examinations or testing (7). Clearly, risks like the infusion of insulin into the veins of healthy children are unlike the sort of risks encountered by all of us in routine examinations or testing. I discuss this definition and various interpretations more fully elsewhere (7).

§46.405

The next category of research is known as "405," again based on its number in the federal regulations. It permits a greater than minimal risk as long as the risks are justified by the anticipated direct benefit to the subject, and if the benefit-to-risk relationship is at least as favorable as that presented by available alternative approaches. In addition, the assent of the subject is needed if possible, as is the approval of parents and an IRB. What constitutes a "direct benefit" is open to interpretation, but is often understood as a direct therapeutic benefit (5). For example, using this category, investigators would be able to compare the efficacy and safety of standard treatments of asthma, cancer, or other diseases. The NICHD obesity study, in contrast, had no likelihood of direct benefit to the subjects; it was done to gain knowledge and so could not be justified under this category.

§46.406

The third category of research, known as "406," allows a minor increase over minimal risks without the prospect of direct benefit to each subject when the subject has a condition (5). "Minor increase over minimal risk" is undefined and, not surprisingly, even wider variation exists about how to understand this definition than exists for "minimal risk." The National Bioethics Advisory Commission (NBAC) (9) and the National Human Research Protections Advisory Committee (NHRPAC) (10) understand a "minor increase over minimal risk" to be just a little more risk beyond what is allowed for healthy children. The NHRPAC includes the following as one-time procedures done with suitable pain relief: a skin punch biopsy, bone marrow aspirate, or lumbar puncture. A central moral and policy question is how can there be a higher risk threshold for some children than for others? I have discussed this in detail elsewhere, but answers require acknowledging two points (2, 7). First, risks of harm and potential benefits for healthy children and children with conditions are often different, and this standard seeks to take this into account, I believe. What is minimal risk for healthy children may be high risk for those with compromised immune systems, and minimal risk for terminally ill children (e.g., discussing loss and death) may be a higher risk for healthy children.

Second, to be consistent with other policies concerning children, I have argued that "minor increase over minimal risk for children with conditions" should be understood as what would be minimal risk for the children with conditions being studied as long as it is understood that the risks for children with medical conditions does not exceed what would be a minor increase over minimal risk for healthy children (2, 7). In addition, to fulfill the 406 category, the research must be likely to yield generalizable knowledge about the child's disorder or condition, which would be knowledge of vital importance for the understanding or amelioration of the disorder or condition that affects the child.

The NICHD investigators and the IRB approving the obesity study apparently believed that having one obese parent constitutes a condition, because it puts these children at some increased risk of becoming obese later in life. OHPR rejected this wide interpretation, as did the Institute of Medicine's Committee on Research Involving Children (1, 11). I have argued elsewhere that "condition" should be understood to be a medical condition and that nowhere is having one obese parent regarded as a medical condition (8). Local IRBs cannot approve studies without direct benefits if they pose more than a minor increase over minimal risks. As noted, the OHRP decided that the obesity study had exceeded this level.

§46.407

The final regulation, known as "407," is a mechanism for gaining approval for research that is not otherwise approvable. Research that is not otherwise approvable must still gain parental permission and the child's assent, if possible, and be approved by the local IRB as presenting a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children. To be approved, the study must also gain the approval of the Secretary of HHS after consultation with a panel of experts in pertinent fields and following an opportunity for public review and comments. The obesity study from NICHD had not gotten the secretary's approval, as OHRP noted in halting it (1).

Wide discrepancy about how to apply these risk categories has existed ever since the regulations were originally issued. In 1981, Janofsky and Starfield (12) surveyed department chairs and pediatric investigators, and found disagreement about how to classify the risk levels of such common procedures as arterial puncture and gastric and intestinal intubation. According to 14% of respondents, puncturing of the eardrum has no more than a minimal risk, 46% stated it had a minor increment over minimal risk, and 40% thought it involved more than a minor increase. An editorial in the *Journal of Pediatrics* (1981) said that this variation demonstrated the need for more consistent risk assessment (13). However, considerable variation about what is permitted still exists (2, 5, 14). Testimony before the NBAC in 1989 revealed that some respondents viewed a lumbar puncture (spinal tap) as posing no more than a minimal risk of harm if done by experts, despite possible risks of headache, infection, nerve damage, and paralysis (9). In contrast, the NHRPAC listed a single spinal tap as presenting a minor increase over minimal risk (10). As we saw, some investigators and IRB members believed that infusing insulin into the veins of children posed minimal risk, and others believed that it presented a minor increase over minimal risk; OHRP believed the risk was higher than this (1).

A New Era of Oversight

Failure to clarify the meaning of the regulations allowed wider and narrower interpretations to flourish unchecked until recently. In this section I will discuss some causes of the change. One measure of the uncertainty among investigators and IRB members about how to understand the regulations was a jump in requests for federal approval of higher-risk studies. After two decades with only two requests for "407" federal approval for studies for which the IRBs believed the risk was too high to approve on the local level, there was a comparative flood (15). Change seems to have been brought on by several factors.

First, there was a shakeup in the Department of Health and Human Services, in which the watchdog committee was taken out of the NIH and set up directly under the Department of Health and Human Services. This new organization, the Office of Human Research Protection, under the leadership of Greg Kosky, began enforcing standards at all research institutions, including the NICHD.

Second, in 1998, the Food and Drug Administration and later the Congress adopted the "pediatric rule," which offers incentives to do pediatric research (11 16). The rule was designed to address the problem that most drugs and products that are in use for both adults and children lack directions for pediatric use on their labels. In addition, the FDA estimated that about 80% of the pediatric drugs used for children are not FDA approved. Consequently, it began requiring sponsors to include pediatric assessments when applying for new drugs or biological products (2). Applicants had to conduct pediatric studies unless they could make a case that the study should not be done. Valid reasons for not doing a study included that the data already existed, the children didn't get the disease, or the drug was especially dangerous for children. Given this incentive, many more pediatric studies began to be planned and done and numerous IRBs, often having few to no pediatric experts, were uncertain how to fulfill federal guidelines (11).

Third, the Best Pharmaceutical for Children Act (BPCA) was passed in 2002 (17). It is a law providing an incentive of six months of extended market exclusivity for companies that conduct pediatric studies. BPCA is a voluntary program and "sunsets" in 2007. Unlike the pediatric rule, BPCA is voluntary, but nonetheless provides great incentives to conduct pediatric studies. A $100,000 investment on a pediatric study, for example, could result in millions of dollars for a drug company gaining exclusivity for six months. The Institute of Medicine has determined that this act should be renewed because it is of great importance (11).

Fourth, two deaths at leading research institutions brought charges that review boards were not protecting subjects properly. Jesse Gelsinger died in September 1999 from a rare liver disease called partial ornithine transcarbamylase (OTC) deficiency (18, 19). This disease causes people to retain toxic levels of ammonia in their blood. Half of all infants with this condition die within the first month. Jesse Gelsinger was more fortunate, and as soon as he turned 18, he eagerly sought participation in a gene transfer trial at the University of Pennsylvania to help advance knowledge about this disease. He had a mild version of the disease, which was being well managed by diet and drugs. Yet he wanted to be a hero, said his father, and so he volunteered for research. Doctors gave him an injection of a normal OTC gene attached to a therapeutic virus. Shortly after this gene entered his liver, he developed a high fever, his blood began to clot, his immune system malfunctioned, his liver hemorrhaged and he died. There were later questions about the quality of his informed consent. Specifically, Jesse and his family had not been told of the deaths of Rhesus monkeys or of patients who had toxic reactions. The investigators and IRB members were also criticized for failing to use the inclusion criteria properly. Later, there were also questions about conflict of interest. Many of the investigators were heavily invested in the company sponsoring the study; thus they had a strong interest in developing the genetic treatment they were investigating, but had failed to disclose this.

In 2002, there was another tragedy at a prestigious institution, Johns Hopkins Hospital, where 24-year-old Ellen Roche died (20). She was a technician at the Asthma Center there and was paid about $350 to enroll in the study and inhale Hexamephonium. According to the consent form, the investigators wanted to find out how “tubes carry air into the lungs” despite the presence of irritating substances. Due to adverse reactions recorded in the 1950s, Hexamephonium had been taken off the market in 1970 and was not FDA approved. Subjects were not told of this or about adverse reactions earlier in the study, and risk level was understated on the consent form. Although Jesse Gelsinger and Ellen Roche were young adults, there was a general concern that IRBs were not doing their job to protect the rights and welfare of research subjects.

Finally, for the first time, the courts rendered decisions having implications for pediatric research policy. In *T.D. v. New York* (21), the court ruled that incompetent persons in a state mental hospital could not be enrolled in research studies having more than a minimal risk. Seen more generally, the decision seemed to support the view that incompetent persons, including children, could not be enrolled in non-therapeutic or no-benefit studies having more than a minimal risk (11). This view was reinforced in the first appellate court case to review the U.S. pediatric research policy, *Grimes v. Kennedy Krieger Institute* (22, 23). This ruling alarmed the pediatric research community, since it seemed to rule out two of the four pediatric categories for research—406 and 407 (Table) (24, 25). It is worth discussing the case in detail, because the investigators and the IRB at Kennedy Krieger Institute (KKI), an affiliate of Johns Hopkins Hospital, were convinced they were acting in the best interests of the children in the study, while the Grimes court compared this research to some of the worst research abuses in recent history, such as the Tuskegee syphilis study. A systematic look at the research and the ruling shows why these perspectives, presumably among reasonable people of good will, were so different.

The KKI study at the center of this dispute was done in the late 1980s and the 1990s; it was called the Lead Abatement and Repair and Maintenance Study (22, 24, 25). Kennedy Krieger investigators had planned the study to find a safe and inexpensive way to remove lead hazards from homes in the Baltimore area. They estimated that 95% of low-income homes in Baltimore had lead hazards. The study focused on five groups of homes, with twenty-five homes in each group. The first three groups were distinguished by the amount to be spent on lead abatement, i.e., repair and maintenance to remove dust, paint or soil containing lead (up to $1,650, up to $3,500 or up to $6,500). Homes in group four had already been extensively abated to make them as safe as possible. Homes in group five were built after 1978, when lead paint was forbidden in homes, although lead hazards might exist in soil or in their neighborhoods.

Parents of two children living in the homes sued Kennedy Krieger. Erica Grimes, in group four, charged that the Institute had found “hot spots” in March and waited until December to tell the family of her elevated blood levels. Her blood levels were 9 on April 9 and 32 on September 15. In addition, the Grimes family charged that they were not told the purpose of the study or the hazards. One of the issues concerns what level of lead poses risks. Lanie Ross, a pediatrician, writes, “The two children whose parents brought suit against the Kennedy Krieger Institute had peak levels of 21 μg/dL and 32 μg/dL.... During the last 30 years, the Center for Disease Control and Prevention (CDC) has revised the blood-level at which lead poisoning occurs, from 60 μg/dL in the early 1960s, to 30 μg/dL in 1975, to 25 μg/dL in 1985, and to 10 μg/dL in 1991. As such, when the research was being done, the researchers should have known that both of these children had blood-levels that posed risks to them” (26, p.55).

The purpose of the study, according to the Maryland Appellate Court, was to compare the efficacy of the abatement with blood levels of lead.

Parents of Myron Higgins, in group two, also sued, claiming that landlords had received a grant for moving a family with young children into a home that had lead hazards. They charged that their child was healthy when they moved in on June 8, 1994. The Higgins family claimed that Kennedy Krieger investigators discovered lead hazards in their home, yet failed to warn them of the danger in a timely way. They also charged that the informed consent was deficient, failing to inform them appropriately of the risks, goals and purposes of the study. Finally, they claimed that the study failed otherwise to prevent the children from being exposed to lead, thus either poisoning the children or putting them at risk of lead poisoning.

KKI was sued for negligence by these parents on behalf of their children. To prove negligence in this case, the parents had to show (a) that the investigators had a duty of care toward the plaintiff, (b) that this duty was breached, and (c) that, as a result, there was an injury or loss. Kennedy Krieger lawyers charged that, as a matter of law, it had no duty of care to the human subjects on the facts alleged by the plaintiffs, and so moved for summary judgment. Even if the children were injured or exposed to risks, KKI lawyers had argued in a lower court, it was not their responsibility to protect the children in the study from unreasonable harm or delays in complete and prompt reporting of potential hazards. The lower trial court agreed with KKI and dismissed the parents' claim, but the decision was appealed on the grounds that there could be a duty of care. The Maryland Court of Appeals reversed the trial court's ruling, stating that the trial court had acted wrongly to grant summary judgment in favor of KKI, because the facts of the case might show that investigators have a duty of care. The court went on to condemn the study, its informed consent document, and the IRB that approved it (22–24).

According to the Grimes court, the informed consent document stated, "We would provide you with specific blood level results. We would contact you to discuss a summary of the house test results and steps that you could take to reduce the risk of exposure" (22, 24). In addition, the consent form failed to state that the study's purpose was to measure the success of the abatement programs by measuring the degree to which the children got lead poisoning, correlating this with the degree of cleanup. Despite the KKI investigators' and lawyers' arguments, the Maryland Court of Appeals found the study to be non-therapeutic. The court was highly critical of the requirement that landlords place children at risk in order to get grants: "The project required that small children be present in the houses. To facilitate that purpose, the landlords agreeing to permit their properties to be included in the studies were encouraged, if not required, to rent the properties to tenants who had young children." The Grimes court concluded that it cannot be in the best interest of a child to be placed at risk in a non-therapeutic study. Specifically, the court stated that "it is not in the best interest of a specific child, in a non-therapeutic research project, to be placed in a research environment which might possibly [be], or proves to be, hazardous to the health of the child.

Initially, the Grimes decision sent shock waves through the pediatric community, because it seemed as if the Grimes ruling held that a non-therapeutic or no-benefit study that carried any risk could not be done (24). This was widely seen as an untenable position, since many important studies, as we noted, are not directly beneficial and carry low risk. But the court later qualified that they meant non-therapeutic studies having more than a minimal risk could not be done (23). They did not view being in an environment where children might get lead poisoning to be a "condition." So the Grimes decision put parents and investigators on notice that, at least in the Maryland district, they are constrained by the Best Interest Standard (requiring that the best of the available options be selected for legally incompetent persons). Grimes ruled that Kennedy Krieger Institute may have owed a duty to warn participants because a special relationship seemed to exist between the parties, because the consent form seemed to create a contractual duty to give this information, because the danger of lead poisoning was foreseeable and well known to KKI, and because a federal regulation exists creating such a duty.

KKI investigators strongly denied that they had done anything wrong. The suit was eventually settled out of court, so we will never know KKI's side of the story (25). The Grimes decision, however, has raised many questions, including: (a) Do investigators and research entities have duties of care to subjects, and if so, when? (b) Can parents legally consent to placing their child in non-therapeutic studies with greater than a minimal risk of harm? (c) What guidelines should exist for informing and notifying parents of children who are subjects about the risks of harm, when doing so would interfere with collecting good data? (d) What is the acceptable level of risk for non-therapeutic (no benefit) pediatric research studies, especially for young children? (e) Is Grimes v. KKI compatible with federal pediatric regulations? and (f) How should other laws and standards, including the Best Interests of the Child Standard, be reconciled with the federal research rules for children (24)? "We have long stressed [that] the 'best interest of the child' is the overriding concern of this court in matters relating to children..." (22, 24). I have argued elsewhere that we should work to find a way to reconcile the pediatric regulations and the "best interest of the child" standard stressed by *T.D. v. N.Y* and the Grimes court (7, 8, 24).

Conclusion

The moral question at the heart of all pediatric research is, how can advances be made to benefit children in general while protecting the rights and welfare of particular research subjects? Research regulations are designed to help address this difficult problem. The U.S. federal pediatric guidelines (5) have been in place for almost a generation, yet key concepts are undefined or so poorly defined that relatively wide and narrow interpretations flourished unchecked until a few years ago. With little direction or consequences, investigators and institutions had little reason to question the authority of their interpretations. Investigators at the NICHD, for example, had been confident that they could safely infuse insulin into children having the "condition" of being at risk for obesity because they had one obese parent.

This situation began to change several years ago. The Office of Human Research Protection, in halting the NICHD's obesity study and stating its reasoning for all to see on the World Wide Web, created a paradigm for others to use in evaluating their own studies. Specifically, they stated that subjects with one obese parent were healthy children and did not have conditions, and that investigators should view hyperglycemic and hyperinsulinemic clamp procedures as posing more than a minor increase over minimal risk of harm (1). Such determinations help clarify what the guidelines mean and limit the plethora of interpretations that have thrived for more than two decades. At the same time, tragic, high-profile events such as the deaths of Jessie Gelsinger and Ellen Roche risked eroding public confidence in the standards used by IRBs to protect subjects' rights and welfare. Yet even as the IRBs were being criticized, there was more pressure on them to approve pediatric studies. Furthermore, the courts were beginning to consider whether the research regulations were consistent with the well-established best interests standard. Guardians cannot consent for studies that put children at risk without direct and compensating benefit. This standard is so engrained in the law that the Grimes court made it clear that if the "best interest of the child" standard is incompatible with the federal pediatric regulations and practices, then the pediatric regulations and practices would have to change, and if federal agencies do not clarify the regulations, the courts will.

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Genetic Testing of Children for Adult-Onset Diseases:

Is Testing in the Child's Best Interests?

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Abstract

Questions related to testing children for adult-onset genetic diseases include many variables that generate different answers among different families. These issues include the biological nature of specific genes, concern about what benefits or harms may accrue from testing children, possible psychosocial sequelae, and ethical and legal concerns about personal autonomy. The shift in the physician-patient relationship from professional beneficence to patient autonomy has established the patient, or parents, as the primary decision-makers in questions about treatment or testing options. The role of parents as decision-makers for their own minor children has been reinforced by four seminal holdings of the United States Supreme Court. Assertions about protecting the future autonomy of children are invalid because minor children are not autonomous. Their parents, on the other hand, have a right—and perhaps even a duty—to exercise their own vested autonomy in making decisions that they believe are in the best interests of their own families. Geneticists are urged to provide clear and complete counseling to parents who seek testing for their children, and then defer to the parents as the primary decision-makers for their own minor children.

Key Words: Genetic testing, children, adult-onset disease.

Introduction

OVER THE PAST DECADE the dilemmas of genetic testing of children have generated much discussion and debate. The controversy first erupted in 1990 when two investigators in Canada asserted that no children should ever be tested for the gene that causes Huntington disease (HD) (1). The rationale offered by these investigators was based on the natural history of the disease, including the fact that HD is an adult-onset, neurodegenerative disease for which there is no treatment or cure. The autosomal dominant gene is fully penetrant, or expressed, and the disease is inevitably fatal. The authors asserted an obligation of professionals to protect the future autonomy of the children. They further asserted that the parents of children who might carry the gene for HD should be treated as third parties with respect to their own children and that decisions about testing should rest with physicians. This last assertion placed the physician squarely between parents and their children.

The responses to the Canadian authors were at first heated and later more measured. The American Society of Human Genetics and the American College of Medical Genetics together designated a task force to examine the issues. The resulting "Points to Consider" paper stopped short of suggesting a complete moratorium on testing children for adult-onset genetic diseases. The task force carefully considered both the benefits and the harms that could result from testing children, including both medical and psychosocial consequences for children as well as their parents. The task force urged thorough genetic counseling for the parents, with the health care provider acting as the advocate for the children's interests. The tone of the joint paper was decidedly cautionary, with clear admonitions to both parents and professionals to consider the options and possible consequences of testing and of using the information generated by testing (2).

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This paper reviews the salient issues in the debate about testing children for genes that cause diseases of adulthood. These issues include the many variables that come into play in making decisions about testing children, recent shifts in the balance of the physician-patient relationship, and the roles of parents, children, and professionals in the practice of genetic testing and genetic counseling.

Variables in Genetic Testing

Decisions about testing children for genes that cause adult-onset diseases are based on a complicated and evolving set of variables. The first and fundamental set of variables relates to the biological nature of the disease of interest. Is the disease caused by a single gene that is readily identifiable, or is the disease the result of a complex interaction of hereditary and environmental factors that are difficult to define and document exactly? If the disease is caused by a single gene, is it caused by a single dominant allele or by a pair of recessive alleles? Has previous research yielded reliable information about the penetrance and variable expressivity of the gene, or genes, in question, and the risks associated with reduced penetrance or a wide range of expression? Is the disease amenable to environmental or medical manipulation? What is the natural course, or severity, of the disease? Answers to these questions will provide basic information about the disease itself and possible pathways for managing the health care of persons who develop the disease (3).

A second set of variables involves the possible costs and benefits that might accrue from testing children for adult-onset diseases. Parents who face the appearance of genetic disease in their offspring may seek to arrange their financial affairs to provide for the inevitable expenses related to medical care and treatment. Indeed, parents may wish to provide trusts for children who will later be affected, so that their unaffected offspring will not be burdened with the costs of caring for affected siblings. Further, parents may wish to relocate their families to centers of specialized research and care for persons who will later develop a difficult condition or disease. While most geneticists agree that providing a medical benefit for children who are tested is the overriding reason for such testing, we must acknowledge that financial and other factors can be of great importance in dealing with the burden of genetic disease.

Geneticists have long recognized the significance of the psychosocial consequences of generating genetic information about children and adolescents. How this information is generated and how it is imparted after testing can have either positive or negative consequences. If the information is carelessly conveyed to children, they may experience depression or loss of self-esteem, and there may be psychiatric sequelae. Children may develop "survivor guilt" based on the knowledge that they may outlive their affected siblings or they may experience a sense of identifying with the family member who will be among the affected. These factors must be taken into consideration when counseling parents both before and after testing, and the discussion should include the possibility of not revealing test results to children at all (4).

A final variable in deciding whether to test children for late-onset diseases is the question of personal autonomy. Some children mature more slowly than others. Children reach autonomy, or the right to make their own decisions, only when they reach the legal age of majority. The child's parents have the legal right to make major decisions for the child until the legal age of majority, with the exceptions of the legal emancipation of a minor or in cases of illegal abuse or neglect. While some professionals claim the right to protect the child's future autonomous interests, they stand at odds with the parents, who should and must exercise their own vested autonomy in making decisions on behalf of their own families.

The Physician-Patient Relationship

The relationship between physicians and patients has evolved significantly over the past several decades. The fiduciary nature of the relationship has traditionally been based on an inherent imbalance between the physician's special training and expertise in medicine and the patient's lack of knowledge, requiring the patient to place considerable faith in the physician's judgment and recommendations. In recent decades, however, as patients have become more curious and informed about their health care, the basis of decisional authority in the relationship has shifted from the physician to the patient. This shift has redefined the physician's fiduciary duty, from a duty to make the best decision for the patient, to a duty to inform the patient about various options so that the patient can make a fully informed decision for himself, herself, or for offspring. Indeed, some professionals in medical genetics have further argued that "[i]n genetics, the patient is really the family rather than the individual, which means that duties to relatives may take precedence over individual rights to privacy" (5).

Roles of Parents, Children and Geneticists in Genetic Testing

Over much of human evolution, parental authority has helped maintain the family as the basic social unit. While the authority of the father over the family was traditionally predominant, women and children have gradually attained the rights of personhood in the eyes of society and the law, and they are no longer regarded as chattel, or property, subject to sale or even death, at the judgment of the husband or father (6). In the United States, in the 20th century, four seminal cases in constitutional law have reinforced the right of parents—fathers and mothers—to make decisions for their own families. The Supreme Court affirmed that the meaning of constitutional "liberty" interests can be extended to include "the right of the individual to contract, to engage in any of the common occupations of life, to acquire useful knowledge, to marry, establish a home and bring up children" (7). A second ruling of the Court found a "liberty of parents and guardians to direct the upbringing and education of children under their control.... The child is not the mere creature of the State; those who nurture him and direct his destiny have the right, coupled with the high duty, to recognize and prepare him for additional obligations" (8). A third case affirmed the right of Amish parents to school their own children after eighth grade, holding that denying this right might create "such an intrusion by the State into family decisions in areas of religious training" that might raise "grave questions of religious freedom" (9). Finally, in the most significant case that arose from the Baby Doe case of the 1980s, the Court affirmed that "[s]tate law vests decisional responsibility in the parents, in the first instance" (10). With these rulings as a foundation, both society and the law give parents wide latitude in their roles as caretakers and decision-makers for their own children, and both society and the law operate from the presumption that parents act in the best interests of their children. These arguments are readily extended to support the right of parents to seek genetic testing for their own children, including testing for adult-onset diseases.

In addition to affirming the role and rights of parents, society has also made significant progress in establishing and protecting the rights of children. The law entitles children to adequate care and the right to live free from abuse or neglect. These rights are supported by both civil and criminal sanctions for violations (11). The value of children in our society is further acknowledged by immunization and other health care programs, by public education and recreation programs, and by "parenting" programs to help parents through the rigors of raising and caring for children. Further appreciation of the rights of children is now evidenced by the tendency to seek the "assent" of more mature children to receive medical treatment or to participate in research protocols.

An important area of concern in the relative roles of parents and children derives from the principle of personal autonomy, or the right to make one's own decisions. Children are not autonomous persons in the law until they reach the age of majority or are legally emancipated. Parents, on the other hand, are by definition autonomous persons; this status is attained either by reaching the age of majority or by legal emancipation following the birth of a child. A significant consequence of parental autonomy is parents' right to make decisions that they believe to be in the best interests of their own children and families. These decisions may include having a child tested for late-onset genetic diseases, thereby allowing both parents and children to explore appropriate options for financial planning and medical management.

Just as the roles of parents and children continue to evolve in applications of our new genetic technologies, so does the role of geneticists change in questions of testing children for late-onset diseases. One of the classic goals of genetic counseling is to help patients "choose the course of action which seems appropriate to them in view of their risk and their family goals and [to] act in accordance with that decision" (12). Viewing the family as the patient, the geneticist helps the family make the best possible adjustment to its genetic situation in view of its values and circumstances. These adjustments may include, for example, decisions to avoid further pregnancies, or decisions to pursue alternative options for having children.

Genetic counseling is often complex and time-consuming, and ideally it is individually tailored to each patient or family. Indeed, counseling is a *process* that may involve several sessions, so that both the counselor and the patients can be assured of a common understanding of all relevant issues. Providing several counseling sessions allows for a flexible protocol and reiteration of points of information that may be reviewed and clarified, as needed, from one session to the next. As well as being an extended process, the *content* of genetic counseling should include information about both the positive and negative implications and consequences of testing children, with thorough discussion about the role of parents in disseminating—or not disseminating—genetic information to children and other family members (13).

Conclusions

Is testing children for adult-onset genetic diseases in the children's best interests? In view of the issues discussed above, the answers to this question become complex and will vary from one family to the next. In general, however, genetics professionals are wise to avoid generating across-the-board rules that may not be in the best interests of the child in all situations. Geneticists should be continually aware that each family represents a unique set of circumstances. The obligations of the geneticist are to present genetic information and its implications in a thorough manner and in understandable language, and to explore with parents the possible options for the family. After clear, careful, and thorough counseling, the genetics professional should defer to the parents as the primary decision-makers for their own families. The final caveat helps the genetics professionals who may occasionally find themselves in situations that are ethically questionable: while professionals are never required to cooperate with requests or activities that are morally repugnant, they may well have an obligation to refer the parents or family to another professional who may be more sympathetic to testing children for adult-onset diseases.

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Why Test Children for Adult-Onset Genetic Diseases?

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Abstract

The genetics community has developed guidelines recommending that predictive testing of children for adult-onset genetic conditions should be withheld. Genetics policy makers have maintained that their restriction of predictive testing of children is justified because (a) it shows respect for children's autonomy and confidentiality, (b) it protects children from harm, and (c) there are no compensating benefits of testing when no effective treatment for the condition is available. Although this approach seems reasonable on its face, a careful examination of the arguments shows that each of the three justifications for restricting testing is flawed. Specifically, I argue that the consensus position is not justified because (a) the appeal to autonomy in this context is baseless and confused, (b) there is no evidence of harm from disclosure, and (c) the claim that there are no benefits from early testing is based on an unjustifiably narrow view of benefits that ignores significant advantages that testing actually provides. Ultimately, for reasons that pediatricians usually consider important, I argue that pediatricians should encourage parents to pursue genetic testing of children at a young age.

Key Words: Genetic testing, predictive testing, adult-onset genetic diseases, genetic diseases.

PERHAPS AS A RESPONSE to the history of eugenics and perhaps as an attempt to distance modern genetics from that history, the community of genetics researchers, clinical geneticists, and genetics counselors has been remarkably proactive in considering the ethical implications of human genetics. They have identified principles for guiding their practice and developed policies, points to consider, and guidelines for helping practitioners to navigate their rapidly developing ethically hazardous clinical domain. As background to their efforts, the genetics community has implicitly endorsed three underlying precepts: (a) genetic information can be a significant medical and psychological benefit to patients/clients, (b) genetic information can help patients/clients to avoid significant harms, and (c) respect for autonomy is of special ethical importance. Based on these presumptions, the genetics community has developed a number of more specific and explicit principles for guiding their clinical practice:

- Tolerance of other reasonable points of view.
- Non-judgmental regard.
- Non-directive counseling.
- Informed consent.
- Confidentiality.

These principles echo the ethical commitments that Western medicine has embraced, and they reflect the current consensus of medical ethics.

Predictive Testing of Children for Adult-Onset Genetic Conditions

As part of their ongoing effort to assure that their practice is ethical, the genetics community has developed guidelines that are specifically relevant to predictive testing of children for adult-onset genetic conditions. In what follows, I shall discuss the recommendations that have been advanced for withholding testing, to determine whether these policies actually conform to their foundational principles. The testing policies that I am particularly concerned with in this discussion relate to genetic conditions for which there is no

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phenotypic evidence for disease at the time of testing (i.e., no signs or symptoms of disease). I shall not be discussing tests that yield ambiguous results, but rather those tests the results of which may indicate a high chance of developing the condition in the future. And I will only consider tests for conditions for which, currently, there is no treatment available to prevent or forestall the development of the condition. In other words, I shall be discussing policies relevant to predictive testing for serious familial conditions in which the family history makes it clear that the child has a very significant chance of developing the disease. I have in mind the testing of asymptomatic children for conditions such as:

- **Huntington's disease (HD)** (an inherited degenerative brain disorder associated with symptom onset and death in early adulthood). When one parent has the disease, a child has a 50% chance of inheriting the affected gene and developing the condition.
- **Polycystic kidney disease** (an inherited kidney disorder associated with kidney failure). When one parent has the disease, a child has a 50% chance of inheriting the affected gene and developing the condition.
- **Familial adenomatous polyposis coli** (an inherited disorder of the bowel associated with a very high incidence of early onset bowel cancer). When one parent has the disease, a child has a 50% chance of inheriting the affected gene and developing the condition.
- **Early-onset Alzheimer's disease** (an inherited degenerative brain disorder associated with symptom onset and death in early adulthood). When one parent has the disease, a child has an approximately 50% chance of inheriting the affected gene and developing the condition.
- **Early-onset breast or ovarian cancer** (an inherited disposition to develop breast or ovarian cancer in early adulthood). When one parent has the disease, a child has approximately a 25–30% chance of developing the condition.
- **Dominant variant of Charcot-Marie-Tooth disease** (an inherited degenerative nerve disorder). When one parent has the disease, a child has approximately a 50% chance of inheriting the affected gene and developing the condition.

Members of the genetics community have expressed their aversion to predictive testing of children for such adult-onset genetic diseases, and in the early 1990s they issued position statements that strongly advised against predictive testing of children for genetic diseases that begin in adulthood (1–3). These position statements do, however, acknowledge that there might be a very few "clear-cut and exceptional circumstances" that could justify testing in a particular case.

Genetics policy makers have offered three reasons to justify their restriction of predictive testing of children for adult onset genetic conditions. (a) They maintain that restricting predictive testing of children for adult-onset genetic conditions is respectful of autonomy and confidentiality because the decision is left to the patient, who will be able to decide when he or she becomes autonomous years down the road. By refusing to perform the test when an immature child and/or the parents request testing of the minor, the geneticist is preserving the decision for the future mature patient. Because the child is not tested now, the grown patient will be able to make the decision about whether or not to be tested and who should have access to the test results (4–6). (b) Geneticists also argue that the tests are harmful in that they carry a significant risk of the "unbearable certainty of knowing," damage to self-esteem, survivor guilt, and injury to the family dynamics. (c) Furthermore, as they see it, these harms are not offset by any benefits, because no effective treatment is available.

Starting in the late 1990s, policy makers and other authors who discuss this matter in the literature have taken remarkably similar positions that differ only slightly from the earlier stand of the genetics community. In fact, those recently writing on this issue have been so consistent in these views that we can count their conclusions as representing an emerging consensus (7–11). In their articles, Cohen (5), as well as Robertson and Savulescu (6), make several telling points. They note that the same hypothetical considerations can result in harms or benefits, that parental authority is an additional important consideration, and that hypothetical harmful outcomes are neither likely enough nor serious enough to justify overriding parental authority. Nevertheless, Cohen, as well as Robertson and Savulescu, conclude that geneticists should only comply with parental requests to test mature children (12–14 years old) who have demonstrated understanding of the tests and their implications and who also want the information (i.e., assent to testing).

What is now commonly recommended is that a decision on testing by the geneticist should be based on the facts of the particular case. In response to a request for testing a minor, and before agreeing to provide the test, a geneticist should begin with an assessment of the minor's competence to make the testing decision for her/himself, compare the benefits and harms of testing, and use that information in deciding whether the testing should be performed. The popularity of this reigning view among clinicians is documented in a report on an international survey conducted by Rony Duncan and colleagues that is described in a 2005 publication in *Genetics in Medicine* (12). Although this approach seems reasonable on its face, I shall be arguing that this consensus position is not justified.

Problems with the Reigning View

Regardless of the genetics community's comfort with their conclusions, and the pediatric community's consensus (13) that

> testing in childhood inappropriately eliminates the possibility of future autonomous choice by the person and risks stigma and discrimination. Unless there is anticipated benefit to the child, pediatricians should decline requests from parents or guardians to obtain predispositional genetic testing until the child has the capacity to make the choice,

a careful examination of their arguments shows that each of their three justifications for restricting testing is flawed. (A) Their autonomy-based justification for not testing children derives from a misunderstanding of the concept of autonomy. (B) There is little or no evidence supporting the postulated harms that are invoked to justify reigning policies. (C) Relevant evidence actually suggests that pediatricians and geneticists would benefit patients and their families by early testing of at-risk children and sharing the results. Together, these considerations suggest that geneticists should generally encourage early predictive testing of children and early communication of test results to the child in an age-appropriate way, although there might be a very few "clear-cut and exceptional circumstances" that could justify not testing in a particular case. I shall explain these thoughts one by one.

A. Autonomy-Related Concerns

Autonomy is the ability to govern oneself and guide one's actions by one's own commitments, goals, and values. Clearly, young children do not have this ability, so the autonomy of a child who lacks decisional capacity cannot be violated by testing the child without consent or assent. We recognize that autonomy is not at issue in medical decisions made on behalf of children whenever doctors and parents impose vaccinations, antibiotic injections or other treatment on children who may scream their opposition.[1] Those who oppose genetic testing of children do, however, argue that parental requests for tests should be rejected because testing a child who lacks decisional capacity violates the principle of respect for autonomy by denying the future adult the opportunity to make the choice for her/himself. They argue that if the child's genetic status is not tested and determined, then the future adult will have the option of deciding about testing.

This line of reasoning misses the most crucial factor in the decision. The child will be raised within a family that shares the experience of the genetic disease.[2] Family members are afflicted, they suffer the disease burdens, and they share their worries about how the disease will progress and their dread of which additional loved ones will succumb. That environment is an unavoidable piece of the child's inheritance. The decision as to whether to raise the child with knowledge or ignorance of her/his genetic status is one that the family must make. Either the testing is not performed and the child is raised without the family and the child having information about whether or not the child has inherited the mutation, or the testing is performed and the family raises the child in the context of knowing that the child has or has not inherited the mutation. Logically, there are no other options. And no child can avoid living through and being affected by the atmosphere in which such a decision needs to be made.

During the period when others must make decisions because the young cannot do so for themselves, those who are responsible for the well-being of children must make decisions on their behalf that reflect altruism rather than self-interest or irrational emotion. If there is a significant difference in the mental health implications of one course over the other, then the promotion of better mental health would be an important reason for parents to choose that course. In the situation of deciding about whether or not to pursue genetic testing of a child for an adult-onset condition, those who choose to leave the decision to the future adult are also actually choosing the course of raising the child in a cloud of dread and uncertainty about their genetic status. That, in itself, is a clear and certain harm.

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[1] Although those who hold the reigning view might invoke imminent risk to justify medical treatment and some vaccinations that they see as a violation of patient autonomy, the justification does not work when the low prevalence of an infectious disease makes contagion and risk unlikely.

[2] Adopted children will be the obvious exception.

Confidentiality is another autonomy-related concern raised by those who defend the consensus view. They argue that testing children for a genetic mutation violates confidentiality. It is true that confidentiality is a vital precept of medical ethics. It is a promise that the health care provider will not disclose information that has been shared under the expectation that it would not be divulged to others without the patient's explicit permission. Confidentiality is critically important in clinical medicine because it encourages open dialogue with health professionals, and because without the assurance of confidentiality health professionals would be less likely to accomplish the good that they aim to achieve on behalf of their patients.

Yet parents' obtaining their child's genetic test results does not violate the principle of confidentiality. When a young child is tested for a genetic mutation, the child is not choosing to conceal or reveal a secret. There is no disclosure of information that the child would only have given up under the promise of confidentiality. Parents decide to authorize taking a sample of their child's blood and having a laboratory perform genetic tests as parents typically authorize such procedures for medical purposes. Also, it is, and should be, standard practice for parents to be provided with medical information about their children, because they need to use it in making decisions about their children's health and well-being. Although one can imagine that some future adults might be unhappy that their parents know about their genetic status, parents' obtaining that information as the result of a test performed in childhood does not involve any violation of confidentiality. Talk of violations of confidentiality in the context of pediatrics may sound significant, but, again, it betrays a misunderstanding of the concept, and in this context it is a "red herring."

Parental authority is the model for making medical decisions on behalf of children. This is a well-accepted social norm that is supported by our laws, and it is usually the most appropriate mechanism for making decisions on behalf of children. Parents are typically deeply concerned with their children's well-being. Parents usually know their children best, at least better than most unrelated policy makers or medical practitioners. Parents also know themselves best. This consideration is important, because it enables parents to incorporate personal knowledge of their own skills, resources, and limitations into their decisions. Also, parents shoulder a very significant portion of the physical, economic, moral, and emotional burdens of the consequences of their decisions. Since they, far more than health care providers or policy makers, are the ones who will be living with the repercussions of their choices, the judgment should be theirs. Furthermore, in situations where different reasonable people can make different decisions, the parents' decisions are most likely to reflect values and priorities that the child will share (14). Overriding the decisions of attentive, caring parents who have decisional capacity can only be justified by "clear-cut and exceptional circumstances" such as avoidance of a very likely and significant harm.

B. Harms

The genetics community lists the "unbearable certainty of knowing," damage to self-esteem, survivor guilt, and injury to the family dynamics as harms that are consequent to genetic testing of children. Although there are differences between children and adults, the evidence at hand is that when adults are tested, regardless of the result and after a relatively brief period of adjustment, they are not harmed by having the information (15, 16).

Recently, Duncan et al. did a survey of clinical geneticists, to muster evidence for such psychosocial harms among children, because, according to their survey of the literature, no previous studies had documented such outcomes (12). They reported on 301 responses between June and September 2003 to their web-based questionnaire; the responses provided details of only 49 cases in which the testing of minors had been performed. Defining "adverse event" very broadly as "any outcome that is potentially negative for the individual involved," they noted that "in three cases parents experienced clinically significant anxiety related to how they would pass on information to their gene positive child." The other two reports of adverse events were experienced by two of the 26 mature minors who received test results. A 17-year-old male who was told that he had an increased risk for HD displayed "initial depression and rebellion but eventual acceptance." A 17-year-old female who was told that she had a decreased risk of HD showed "no psychological disturbance but worry and responsibility for affected mother and untested brother."

Not to diminish or discount these discomforts in any way, it is, however, important to remember that it is common and reasonable to consider untoward effects in the context of beneficial effects. The upset and discomfort of the vaccinated child is evaluated in the context of the immediate and distant risks and pains that are prevented for that child and for others. And in comparing positive and negative outcomes we have to recall the kinds of lessons that Jeremy Bentham taught long ago, and avoid oversimplified calculation (17). There can be important differences in the certainty of the outcome, the intensity of the reaction, the duration, the likelihood of it being immediately combined with some additional positive or negative outcome, or being followed by other positive or negative outcomes. We have to consider the likelihood and extent of positive outcomes in order to justify foreseeable negative outcomes. If there are no direct positive psycho-social outcomes of testing children for an adult-onset genetic disease, then a small risk of an adverse outcome has to be considered in light of the importance of defending parental discretion. That said, the adverse events reported in the Duncan study hardly amount to harms that are significant or likely enough to justify a policy that denies testing.

Nevertheless, the most significant finding of the Duncan study is that clinicians continue to endorse the testing guidelines. There is a further result that can be gleaned from the study that the authors do not seem to notice. Although the survey was sent (and re-sent) to clinical geneticists in the US, the UK, and Australia, the anonymous respondents reported only 22 cases of the testing of immature children and 27 cases of the testing of mature children. These very low numbers of tests suggest that, to a very significant extent, the guidelines have become a standard of care. They actually govern the behavior of clinical geneticists and they inhibit the testing of children. This result in turn raises the question of whether medicine is justified in adopting a standard of care that is not supported by evidence.

Furthermore, we know that children and their families can and do cope with tragic genetic information without being devastated by the news or overcome by the burden. Children adapt to obvious familial disorders, such as hemophilia, that may afflict them in childhood. Children with terrible and handicapping conditions, such as paralysis, diabetes, or epilepsy, are also able to accommodate to that information. In that light, it is reasonable to ask whether the "unbearable certainty of knowing" is a credible concept or a genuine harm that should count as a reason for refusing to provide genetic testing. Again, children can and do cope with serious and even fatal diagnoses of diseases such as cancer, end-stage organ failure, and AIDS.

Affective Forecasting, Durability Bias, and Focalism

The fact that the genetics community has, without supporting evidence of harms, adopted, supported, and adhered to its strong policies on testing children invites speculation. Recent work in cognitive psychology on unwanted and invisible influences on judgment provides important insight into this peculiar phenomenon. A series of papers by Timothy D. Wilson and Daniel T. Gilbert and colleagues offer a framework for making sense of the genetics community's position (18–22). Although they take circumstances such as predicted reactions to football games, elections, and tenure decision as their examples, their points are relevant to any situation where decisions are based on predicted reactions.

Through a number of studies, Wilson, Gilbert and others demonstrate that judgments of future mental states are contaminated by various distortions (18–22). People systematically focus primarily on the negative reactions to a future event while largely ignoring other outcomes (focalism), including their ability to generate satisfaction with whatever outcomes come to pass, and they over-predict the duration of their negative emotional reaction to future events (durability bias) and hence reach unjustified and slanted conclusions about their own emotional responses to future events (affective forecasting) and to those of others (18–22). The robustness of these findings suggests that everyone is vulnerable to affective forecasting biases, including patients, parents of patients, and clinical geneticists.

Those who developed the policies on genetic testing of children for adult-onset conditions appear to have behaved just as Wilson and Gilbert would have predicted. That is, they probably focused their attention primarily on the possible negative emotional reactions following disclosure of testing results to a child or a family, and overlooked the advantageous outcomes, as well as people's natural ability eventually to reconstruct the outcome as something good. These normal cognitive distortions may have also led the drafters to over-predict the duration of the emotional reaction of children and their families and, in turn, inclined them toward untenable policy conclusions.

C. Unappreciated Benefits

The genetics community has asserted that genetic testing for adult-onset diseases provides no benefit to the tested child. But they may have overlooked possible benefits, and also some harms that could be averted by testing. As I have defined my topic, there is currently no beneficial medical treatment available for the conditions we are considering. Yet, other, non-medical advantages can be expected to follow from genetic testing and a variety of harms could be avoided by providing the tests.

There is accumulating evidence that uncertainty is worse than even bad news, and that the stress of uncertainty correlates with negative effects on the psycho-neuro-endocrine-immune system (23–26). For example, the vast majority of those tested for HD find the uncertainty of not knowing their genetic status to be more burdensome than receiving either a negative or positive test result (23–26). Similarly, children who have cancer cope better with specific and frank disclosure of information than with non-disclosure and uncertainty (26). From that perspective, almost everyone who is tested can benefit, at least by being relieved of uncertainty. Furthermore, in the examples listed above, 50–75% of those tested would also get the good news that they are unaffected. I take those odds alone to be an overwhelming reason for testing children.

Furthermore, other pediatric literature and policies acknowledge that deceiving or withholding information from children can be harmful (23–26). In fact, the American Academy of Pediatrics (AAP) has issued policies recommending that children be informed by the time that they enter school about their being adopted (27) and about their being HIV+(28). For example, the AAP position statement on adoption recommends that,

> Even before a child understands the words “adoption,” “adopted,” and “biological family” or “birth family,” it is important that these words be a part of a family’s natural conversation.... Families should be discouraged from “waiting until just the right minute” to tell children that they were adopted, because this may leave children feeling betrayed and wondering what else their parents may have hidden from them. Children may also learn information from peers or neighbors, which may impair the trust between parent(s) and child. It is important to share with even very young children their adoption story.... An honest approach in the discussion...will give a child permission to ask questions or to make statements about adoption and at the same time will take away the veil of secrecy that often implies that being adopted is a negative condition.

Similarly, the AAP has endorsed a policy of informing children that they are dying (29). And in a similar vein, authors such as McGee et al. (30) and Haimes (31) have argued that children should be told that they were created with gamete donation as soon as they are able to understand. These positions are based on compelling reasons that are also applicable to the case of genetic testing of children for adult onset diseases.

Generalizing from what we already know about these analogous situations, we can expect that withholding testing can be harmful. We can also surmise that testing early and informing children of test results can prevent problems that are likely to arise from delaying testing until the children are old enough and mature enough to make a decision for themselves. There are some general considerations for testing and informing children that apply to many situations:

- When all of the adults involved know that a child is at risk, non-disclosure creates an environment of tension and discomfort that the child is likely to pick up and translate into a sense of insecurity. Learning the information early on is likely to avoid these problems.
- Information becomes part of identity. When a child learns personal genetic information early in life, it can be absorbed and accommodated into identity. When the information is disclosed later in life, it can be jarring to identity and very hard to internalize and accept.
- Putting off the testing decision until late adolescence compels the child to live through many years of uncertainty. It also pushes off the testing decision and its consequences into adolescence, compounding the trauma of those years.

Additional considerations for the parents and for the child are especially relevant to genetic testing for adult-onset conditions. Delays in learning a child’s genetic status prolong parents’ uncertainty and anxiety. From surveys of parents, we know that they identify worries about when and how to tell a child and anguish about the aftermath of the conversation as a significant burden. Delays in testing increase their dread of having to speak about the matter with their child, and that makes the hurdle of latter disclosure seem more and more formidable. The prolonged period without testing also delays their learning how to speak frankly about the genetic condition. When parents begin speaking about it when the child is very young, they have the chance to become comfortable with the discussions as the child matures.

Putting off testing until the child reaches late adolescence can also be expected to have a negative impact on the child. The delay amplifies the dread and increases the hurdles for the child who anticipates developing a familial disease, and these magnified impediments set the stage for a crisis when the information is ultimately disclosed. Refusing testing to children also delays the child’s learning to speak about her/his condition and accommodating to it. Avoiding these formidable and likely harms to parents, children, and their relationships amounts to a significant benefit.

Evidence from adult testing for HD provides a further consideration that is relevant to assessing the benefits of early testing. Only 10–15% of at-risk adults opt for Huntington's disease genetic testing. Studies of those who were tested provide relevant and important data. Some untoward results followed reports of both good and bad news. People were upset, but over time, most did come to accept the information and most were glad that they were no longer in ignorance. People also behaved as affective forecasting would have predicted. Because people tend to exaggerate the impact of bad news, many of those who did not know their HD status before testing had acted as if they would develop the disease, and they had made choices about reproduction, finances, education, and career in that light. In other words, they had made decisions and foregone opportunities as if they were certain to develop the disease. I take this as a very significant and avoidable harm. If it can be averted for 50–75% of the children who are at risk for inheriting a serious genetic disease, it is important to amend policy in that light.

Conclusion

Geneticists often state the principle that we are an amalgam of our genes and our environment. In other words, the adult someone ultimately becomes is the product of both her genetic inheritance and the conditions and influences of her life. While there is currently nothing that we can do to alter someone's genetic endowment, we can take steps to modify the environment in which a child is raised so as to optimize her accommodation to her genetic heredity and diminish the risk of confounding the problem. The possible benefits of doing so make it ethically important to avoid psychological traps and make policy decisions about genetic testing of children based on available information and sound reasoning.

An important principle in ethics is that honesty is usually the best policy. Another is that knowledge is usually better than ignorance. Both of these precepts are obviously applicable to the question of whether children should be tested for adult-onset genetic disease. They point to the conclusion that such testing should be done.

In addition, the arguments that have been advanced to oppose testing seem unpersuasive when they are carefully examined. (A) The appeal to autonomy is baseless and confused. (B) There is no evidence of harm from disclosure. And (C) the claim that there are no benefits to be had from early testing and early informing is based on an unjustifiably narrow view of benefits that actually ignores factors that the AAP considers very significant in other contexts.

All of these factors, taken together, lead me to a conclusion that is diametrically opposed to the policies and guidelines of the genetics and pediatric communities. Based on the considerations I have outlined above, and the models of well-reasoned position statements on similar issues of testing and disclosure, I conclude that pediatricians and geneticists should encourage parents to pursue genetic testing of children at a young age. They should also strongly recommend the involvement of genetic counselors for the education and support that they could offer. Furthermore, they should strongly advocate for early disclosure of test results, show understanding of the anticipatory fear that parents are likely to experience, and provide guidance to help parents learn to speak openly with their children about their genes. Ultimately, however, because parents are in the best position to assess their own emotional state and ability to cope with the test results, because of the social importance of yielding to parental discretion, and the fact that the future is long, I would advise doctors to leave the actual decision to parents.

The fact that so many thoughtful and well-intentioned authors of medical policies have reached erroneous conclusions on this issue tells us that the power of affective forecasting makes it very hard to see the light. Pediatricians and geneticists should encourage reluctant parents to have their children tested—and then accept the parents' decision.

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Endobronchial Pulmonary Nocardiosis

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Abstract

In recent years, the reported incidence of nocardiosis, a localized or disseminated infection caused by *Nocardia*, has been increasing. This increase can be attributed to the improvements in diagnostic capabilities and the higher clinical index of suspicion, as well as the increased prevalence of immunosuppressed patients.

We report a case of pulmonary nocardiosis in a healthy young female who presented with cough and hemoptysis, which persisted even after empiric treatment for pulmonary tuberculosis. CT scan of her chest showed infiltrates in the right upper, middle and lower lobes with pleural effusion. Bronchoscopy revealed a friable endobronchial mass. Special stains confirmed the diagnosis of nocardiosis. The patient's symptoms and clinical findings improved with trimethoprim-sulfamethoxazole. To the best of our knowledge, this is the fourth case of this illness presenting as endobronchial mass reported in the literature. Pulmonary nocardiosis should be considered in the differential diagnosis of hemoptysis, even in immunocompetent patients.

Key Words: Nocardiosis, endobronchial mass, immunocompetence.

Pulmonary nocardiosis is a rare infection; however, its reported incidence appears to be increasing. This is probably due to a higher degree of clinical suspicion, increased use of immunosuppressive treatments and the appearance of AIDS (1, 2). The disease presents with a highly variable clinical and roentgenographic picture that can mimic granulomatous disease or neoplasm (3–5). Thus, it is often misdiagnosed as tuberculosis, invasive fungal infection or cancer. Although nocardiosis usually occurs in immunocompromised hosts, it has also been occasionally reported in immunocompetent patients (6, 7). A review of the literature reveals only three previously reported cases of pulmonary nocardial infection presenting with an associated endobronchial mass, as in the case reported here.

This article describes the clinical course of pulmonary nocardiosis in a healthy young female, who was initially misdiagnosed as having pulmonary tuberculosis.

Case Report

A 25-year-old female Hispanic immigrant was referred to our clinic for evaluation of persistent cough and hemoptysis. The patient reported a 5-year history of persistent cough and pleuritic chest pain. The cough was usually productive of greenish sputum, but occasionally frank hemoptysis was noted, including two episodes of coughing up approximately 250 mL of blood. Initially the patient continued normal activities and denied any fatigue or dyspnea, but she subsequently developed worsening dyspnea on exertion. She denied weight loss, joint pain or fever. Hospitalized multiple times for treatment of recurrent pneumonia, she had repeatedly tested negative for the HIV virus by serology, and sputum staining for acid-fast bacilli was negative on multiple occasions.

The patient was empirically treated for pulmonary tuberculosis (TB) with six anti-TB medications for six months. Her symptoms progressed despite the empiric anti-TB treatment. She is a non-smoker and has no history of substance abuse. In the clinic, physical examination revealed a

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young female in no distress and without adenopathy, clubbing or oral lesions. Her chest was clear to percussion and auscultation. Heart sounds were regular without murmur. There was no hepatosplenomegaly. She was neurologically intact. Her total white blood count was 6.1 mm^3 with lymphocytes 43% and neutrophils 41%. She had a high erythrocyte sedimentation rate of 81 mm/hr. Serum chemistry levels were normal, including an angiotensin-converting enzyme level of 13 U/L. Electrocardiogram showed normal sinus rhythm. A computed tomography (CT) scan of chest with contrast showed infiltrates in the right upper, middle and lower lobes with a right pleural effusion (Fig. 1). Bronchogenic carcinoma with obstructive pneumonitis was suspected, based upon the clinical and radiological findings. A fiberoptic bronchoscopy was performed, revealing a friable right lower lobe posterior segment lesion appearing "pearly white," with irregular borders and completely occluding the entire segment (Fig. 2). Pathology revealed bronchial mucosa with extensive acute and chronic inflammation and numerous eosinophils. Staining with methenamine-silver was consistent with *Nocardia* (Fig. 3). The patient was started on trimethoprim-sulfamethoxazole.

The patient's cough and sputum production gradually resolved. Repeat CT scan a month later showed disappearance of the pleural effusion and partial clearing of the pulmonary densities (Fig. 4).

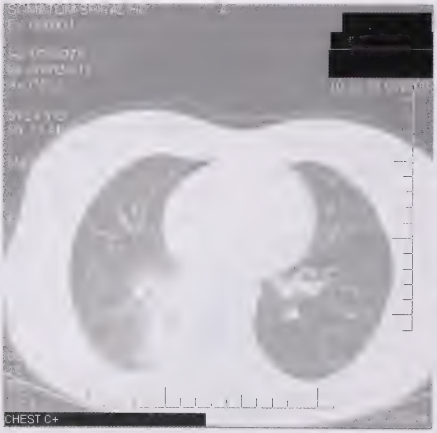

Fig. 1. CT scan of chest with contrast, illustrating infiltrates in right upper, middle and lower lobes with a right-sided pleural effusion.

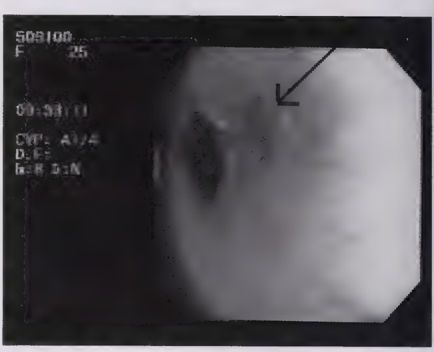

Fig. 2. Photography during bronchoscopy, showing the lesion in the right lower lobe (arrow).

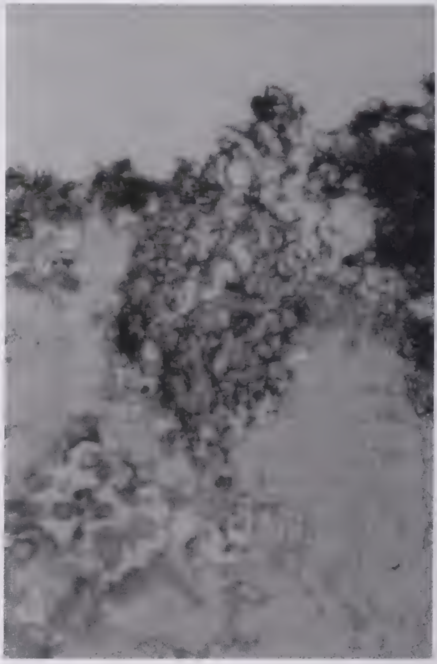

Fig. 3. Gomori methenamine-silver stain, demonstrating black filamentous *Nocardia* (magnification ×400X).

Discussion

Our immunocompetent patient had pulmonary nocardiosis, which presented as nonresolving pneumonia.

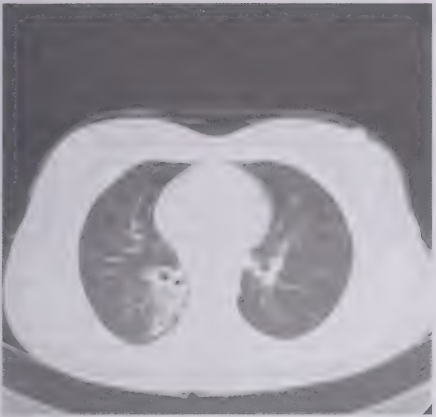

Fig. 4. Repeat chest CT scans, showing disappearance of pleural effusion and resolving pulmonary densities.

Nocardia is characterized by aerobic, gram-positive, variably acid-fast, non-motile, non-spore-forming, branching filaments (6). Found in soil and vegetation, the organism is most virulent when inhaled. As a result, pulmonary infection is the most common form of the resulting disease. Hematogenous spread to other organs is also possible, especially in immunocompromised persons (3, 6). There are no known cases of person-to-person transmission (5). Clinical suspicion is crucial, since most antibiotics commonly used to treat pneumonia are ineffective against it. Delay in diagnosis is common (8). Pulmonary nocardiosis can be acute, subacute or a chronic suppurative infection (1). The clinical manifestations of pulmonary nocardiosis are nonspecific and include productive cough, fever, night sweats, anorexia, generalized malaise, chest pain and hemoptysis (6). Classic pneumonia, lung abscess, or cavitary disease with spread to contiguous structures are also typical clinical presentations.

Pulmonary nocardial infection is not usually considered in the differential diagnosis of an endobronchial tumor. Moreover, expectorated sputum may or may not yield positive smears or cultures even in established pulmonary infection. Various invasive procedures for obtaining specimens, including bronchoscopic biopsy, percutaneous lung aspiration and open lung biopsy, may be needed to make a definitive diagnosis. Brown et al. (9) described a 28-year-old man who was found, on fiberoptic bronchoscopy, to have a large fungating mass extending into the right main stem bronchus. Two additional bronchoscopies and a mediastinotomy were required before a diagnosis of nocardiosis was made. Even though *Nocardia* will grow in routine bacterial culture media in approximately 2–14 days, bacterial cultures of pulmonary secretions are discarded after 48 hours, and therefore an opportunity for identification of *Nocardia* colonies will be missed. The microbiology laboratory should always be notified, so that culture techniques for the isolation of *Nocardia* are used. Sulfonamides remain the initial treatment and the mainstay of therapy for *Nocardia* infection (1, 10). The optimal duration for therapy is not clear, but most authors recommend 6–12 months of treatment at a minimum (1, 5).

We caution that this potentially treatable disease may be mistaken for tuberculosis, especially in immunocompetent patients, for whom the index of suspicion is low.

This case also underscores the importance of considering infectious processes as a cause of nonresolving lung opacities.

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Erythrocytosis in a Scleroderma Patient

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Abstract

A 40-year-old black male with scleroderma lung disease presented with blurry vision and headache. His presenting hemoglobin was 22.3 g/dL and his serum erythropoietin level was surprisingly low. Although nocturnal hypoxemia was evident, his daytime resting arterial oxygen saturation was normal. The patient's symptoms of hyperviscosity improved after phlebotomy, as his hemoglobin gradually decreased to 18.3 g/dL. Repeat serum erythropoietin levels were in normal and high ranges. Patients with chronic interstitial lung disease and erythrocytosis could have normoxemia at rest and a normal or low serum erythropoietin level at the peak of erythrocytosis. A repeat sampling of serum erythropoietin and monitoring of oxygen saturation during sleep and exertion may help in diagnosis. Physicians should prescribe continuous oxygen therapy for patients with chronic interstitial lung disease and erythrocytosis, even if diurnal resting hypoxemia is absent.

Key Words: Scleroderma lung disease, erythrocytosis, erythropoietin, polycythemia vera.

Introduction

ERYTHROCYTOSIS is a not uncommon complication of chronic hypoxic lung disease, yet it has rarely been reported in scleroderma patients. This heightened erythropoietic activity is thought to be an erythropoietin-dependent, compensatory response to hypoxia. We report an unusual case of erythrocytosis secondary to scleroderma lung disease with a low serum erythropoietin (sEPO) level.

Case Report

A 40-year-old black male presented with blurry vision, headache, and left lower extremity pain for 3 days. He had a history of scleroderma complicated by pulmonary fibrosis and pulmonary hypertension. Admitting physical examination was notable for a cyanotic, erythematous, and mildly tender left foot. Laboratory data revealed that his hemoglobin was 22.3 g/dL, hematocrit 72.8%, white cell count 3,300/μL, and platelet count 199,000/μL. His daytime arterial oxygen pressure (PaO_2) was 70 mm Hg with an oxyhemoglobin of 93% on room air by co-oximetry, while his nocturnal oxygen saturation by pulse oximetry ranged from 88–90%. His sEPO level on admission was surprisingly low at 3.3 mIU/mL (reference range: 4.2–27.8). Both leukocyte alkaline phosphatase scores and serum vitamin B_{12} levels were within reference ranges. Pulmonary function tests indicated severe restrictive ventilatory defect. Chest and abdominal CT showed extensive interstitial thickening with peripheral honeycombing in bilateral pulmonary parenchyma consistent with diffuse pulmonary fibrosis, but no hepatosplenomegaly or mass lesions. A diagnosis of secondary erythrocytosis (SE) with erythromelalgia was made. In addition to supplemental oxygen, aspirin and intravenous hydration, phlebotomy was performed daily. The patient's symptoms of hyperviscosity soon improved, as his hemoglobin and hematocrit gradually lowered to 18.3 g/dL and 56.1%, respectively, after 8 sessions of phlebotomy. The patient's sEPO level was now 24.2 mIU/mL. He was discharged on continuous low-flow oxygen therapy. Follow-up hemoglobin and hematocrit 10 months later were stable at 18.6 g/dL and 56.4%, respectively, with an sEPO level of 71.4 mIU/mL.

Discussion

Our patient had an unusually high hemoglobin level at presentation. Extensive evaluation substantiates our initial impression that he had an acquired erythrocytosis secondary to his underlying scleroderma lung disease. Despite the initial "inappropriately" low sEPO value, polycythemia vera (PV) was unlikely, since both leukocyte alkaline phosphatase and vitamin B_{12} levels were normal, and the patient did not have splenomegaly or leukocytosis nor thrombocytosis.

Although a polycythemia vera study group did not include a low sEPO level as one of the diagnostic criteria for PV, measurement of sEPO has since been embraced in the polycythemia work-up (1, 2). Generally, sEPO levels in PV are low, while those in SE are expected to be high since SE is a hypoxia-induced, EPO-driven process. However, using sEPO measurement alone provides a poor sensitivity in diagnosing either PV or SE, due to the considerable overlap of the sEPO values in dif-

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ferent erythrocytoses (1, 2). About half of the patients with either PV or SE could have an sEPO level well within reference ranges. Moreover, even though the specificity of a low sEPO level in diagnosis of PV is extremely high, false-positives can occur, as in this case and those reported by others (1, 2). Low sEPO values in the setting of SE are usually associated with high hemoglobin levels. This underscores the need for a repeat determination of sEPO values when treatment lowers the hemoglobin. In our case, the sEPO levels rebounded from a low pretreatment level to a high normal level after phlebotomy, and became elevated 10 months later, while the hemoglobin remained stable. These observations suggest that there is a built-in negative feedback control for regulating sEPO production, and this control mechanism appears to remain intact even at high hemoglobin levels. Thus, hypoxia at tissue and cellular levels would initiate a cascade of intracellular events leading to an increased production of sEPO, which in turn expands the red cell mass (RCM); the resultant elevation of oxygen delivery would then correct the hypoxia and turn off the triggering stimulus.

Although RCM is probably a more sensitive gauge of erythropoietin stimulation, clinically, hematocrit is often used as a surrogate for RCM because of their linear relationship (3). Increased hematocrit, especially if >60%, is usually associated with an increase in RCM. However, in patients with hypoxic lung disease, RCM can be misrepresented by hematocrit or hemoglobin because plasma volume tends to expand due to complicating pulmonary hypertension and/or right heart failure (4). Therefore, high normal hemoglobin levels in our case may be deceiving and the RCM may well be elevated, which would be consistent with the elevated level of sEPO.

Given the extent of pulmonary involvement and the erythrocytosis in this patient, normoxemia at rest was unexpected and initially puzzling. In general, hypoxemia and RCM are linearly related in normal people (3). However, in patients with chronic hypoxic lung disease, the degree of hypoxemia does not always correlate well with RCM. This poor association is not completely understood. Hypoxemia is often determined by isolated "snapshots" of arterial oxygen percent saturation (SaO_2) or PaO_2, which probably do not reflect overall oxygenation accurately in this group of patients. This point is supported by the observation that, despite adequate arterial oxygen saturation during wakefulness at rest, patients with chronic interstitial lung disease (ILD) can have brief, recurrent episodes of hypoxemia during sleep or after vigorous exercise (5). In addition, polycythemic patients with hypoxic lung disease were reported to have more severe and more frequent hypoxemia than their nonpolycythemic counterparts did (6). These findings indicate that transient hypoxemic episodes during sleep and exertion are pathophysiologically relevant, and can be a robust stimulus for EPO-mediated erythropoiesis (7).

It is interesting to note that sEPO levels in our patient stayed elevated, even though his hemoglobin remained at normal high levels, and his hypoxia was presumably corrected with continuous supplemental oxygen. It is possible that even in patients receiving continuous low-flow oxygen therapy, situational hypoxemia during sleep and exertion (or due to occasional medical noncompliance) can still occur. Furthermore, while extremely high hemoglobin is a potent suppressor for sEPO production, leading to a low or normal sEPO level via negative feedback, high normal or marginally elevated hemoglobin is not. Therefore, if these intermittent periods of nocturnal or exercise-induced desaturation continue to exist, sEPO levels can remain high.

Conclusion

Patients with chronic ILD complicated by erythrocytosis could have a low sEPO value and normal resting arterial oxygen saturation that may misleadingly suggest a diagnosis of PV. A repeat sampling of sEPO and monitoring of oxygen saturation during sleep and exertion may help to clarify the diagnosis. Practicing physicians should prescribe continuous oxygen therapy for patients with chronic ILD and erythrocytosis, even in the absence of diurnal resting hypoxemia.

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Genotypic Characterization of *Helicobacter pylori cagA* and *vacA* from Biopsy Specimens of Patients with Gastroduodenal Diseases

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Abstract

Background: *Helicobacter pylori* infection is closely associated with gastroduodenal diseases. *H. pylori* infection with different *vacA* and *cagA* genotypes may result in divergent consequences. The aim of the present study was to investigate the prevalence of *H. pylori* infection and the correlation between *cagA* and *vacA* genotypes with the consequences of *H. pylori* infection in Taiwan.

Methods: Genomic DNA from 97 gastric biopsies of patients with various gastroduodenal diseases was collected, and the prevalence of *H. pylori* infection, *cagA* genotypes and *vacA* genotypes, was analyzed by polymerase chain reaction. In addition, the correlations between *cagA* and *vacA* genotypes and the consequences of *H. pylori*-infection were statistically examined.

Results: Our results indicated that 57.7% of this sample of patients with gastroduodenal diseases were infected with *H. pylori*. Prevalence of $cagA^+$ strain in *H. pylori*-infected patients was 71.4%. All of the genotypes of the $cagA^+$ *H. pylori* strains among our patients were type A. Prevalence of *vacA* signal region s1 and middle region m2 genotype in *H. pylori*-infected patients was 98.2% and 53.6%, respectively.

Conclusions: Our study demonstrated that individuals infected with *H. pylori* strains that carried *cagA* gene and *vacA* s1/m2 genotypes were associated with the development of gastroduodenal diseases, compared to those infected with $cagA^-$ gene and $vacA^-$ *H. pylori* strains.

Key Words: *Helicobacter pylori, cagA, vacA*, gastroduodenal diseases.

Introduction

HELICOBACTER PYLORI is a curved, microaerophilic Gram-negative bacterium. Much evidence in epidemiological, pathological and animal experiments indicates that *H. pylori* infection can result in gastritis or gastric cancer. Approximately 50% of people worldwide are infected with *H. pylori* (1, 2). The prevalence of *H. pylori* infection in developing countries is as high as 70 – 90% (3), whereas that in Europe and the U.S. is usually less than 10% (4). These surveys demonstrate that environmental and racial differences can result in different rates of *H. pylori* infection.

Vacuolating cytotoxin gene A (*vacA*) and cytotoxin-associated gene A (*cagA*) are two of the most important *H. pylori* pathogenic factors (5); *cagA* can be a marker gene to detect peptic ulcer (6). About 60 – 70% of *H. pylori* isolates in Western countries are $cagA^+$ strains (7); however, more than 90% of *H. pylori* isolates in Asian areas are $cagA^+$ strains (8 – 11). The *cagA* gene can be classified into type A, B, C and D, according to the appearance of specific types and numbers of its 3′-terminal repetitive sequences designated as R1 (repeat sequence 1, 15 bp), R2 (42 bp) and R3 (147 bp) (11). Ninety-five percent of *cagA* from isolates of Japanese patients with gastric ulcer and duodenal ulcer are type A genotype (11). However, only 50% and 76% of *H. pylori* from patients with gastric ulcer and duodenal ulcer among Western countries, respectively, carry type A genotype (11).

VacA can induce host cell vacuolation and eventually cell death (12). A high degree of sequence variability also exists in the *vacA* gene. The signal region of *vacA* gene can be classified as s1, which can be further classified into s1a and s1b, as

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well as s2 subtypes. The middle region of *vacA* gene can be divided into m1 and m2 subtypes. Different subtypes of these 2 regions combine in different strains to form mosaic genotypes (13, 14). Genotypes of s1/m1, s1/m2 and s2/m2 are more prevalent in Western countries (13, 15–17). The frequency of s1/m1 and s1/m2 genotype is approximately half, respectively, in isolates from Central America, North America and Europe, while s1/m1 genotype is more prevalent in South America and Spain (13, 15, 18). In Asian areas, s1a/m1 genotype is most prevalent in Japan (19), but s1a/m2 genotype is more frequent in mainland China (20).

As described above, ample evidence demonstrates that differential *vacA* and *cagA* genetic characteristics exist in *H. pylori* strains isolated from different geographical regions. Therefore, using molecular techniques to study the correlation of *H. pylori* genotypes or strains with gastroduodenal diseases has become an important study subject. The current study attempted to identify the frequency of *H. pylori vacA* and *cagA* genes in Taiwanese patients with gastroduodenal diseases, using gastric biopsy for analytic target samples. The putative association of *vacA* and *cagA* genotypes with the consequences of *H. pylori* infection was also examined.

Materials and Methods

Study Subjects and Samples

Gastric biopsies from 97 patients referred for upper gastrointestinal tract endoscopy with gastritis, gastric ulcer and duodenal ulcer in the Department of Gastroenterology in Taichung Veterans General Hospital were collected. Written consent was obtained from all the study subjects after the nature of the procedure was explained. The protocol for the research was approved by the Ethics Committee of Hung Kuang University. Basic information on the study subjects is given in Table 1.

Tissue Preparation and PCR Reactions

Gastric biopsies from all the study subjects were stored at temperatures under −70°C until use. Each biopsy was digested with tissue extraction buffer (50 mL Tris-HCl, pH 8.0, 1 mM EDTA, 0.45% Tween 20, 0.45% Nonidet P-40 and 100 μg/mL proteinase K) at 55°C for 3 hours. Then 200 μL of phenol was added to tissue lysate to extract genomic DNA. Genomic DNA was subsequently quantified for polymerase chain reaction (PCR) reactions. PCR amplifications were carried out in 15 μL PCR reaction mixture containing 50 ng of genomic DNA, 1 μM of specific primers for each target gene amplified (Table 2), 1.5 μL 10x Failsafe™ PCR buffer (Epicentre Tech, Taiwan) and 1 unit of Taq DNA polymerase, using PCR thermocycler (PCR system 9700, Perkin Elmer). Amplified fragments were separated in 2% agaorse gel and visualized under ultraviolet transluminator. PCR genotyping of each biopsy was carried out at least twice to confirm the credibility and reproducibility of genotyping results.

Statistical Analysis

Results were analyzed by using SPSS software. The association between different groups of patients and *H. pylori* genotypes was analyzed by Pearson Chi-Square test with Yates's correction. The Mann-Whitney test was used for assessing correlation between various *H. pylori*-related diseases and concurrent presence of *cagA* and *vacA* genotypes. Significance was indicated by a two-tailed *p* value of less than 0.05.

Results

Prevalence of *H. pylori* infection was detected by PCR techniques using *H. pylori* 16S rRNA-specific primers (16S-1 and 16S-2, Table 2) as described by Warburton et al. (17). The prevalence of *H. pylori* infection in our patients was 57.7%

TABLE 1

Clinical Diagnosis and Frequency of H. pylori Infection (16S rRNA) among Subjects in This Study

Diagnosis	**Sample**	**Age**		**Sex**		***H. pylori* (16S rRNA)**	
	n	**Range**	**Mean ± SD**	**Male**	**Female**	**Positivity**	**n (%)**
Gastritis	11	21–66	41 ± 17.20	7	4	4	(36.4)
Gastric ulcer	66	17–88	57 ± 14.32	46	20	37	(56.1)
Duodenal ulcer	20	21–88	58 ± 15.30	12	8	15	(75.0)
Total	97	17–88	52.5 ± 15.61	65	32	56	(57.7)

TABLE 2

Primers Used for Amplification of the H. pylori 16S rRNA, cagA and vacA Genes

Designation	Target sequence	Primer sequence	Annealing condition	Size (bp)	Ref
16S-1	16S rRNA	5′-GCTAAGAGATCGGCCTATGTCC-3′	55°C, 60 sec	522	17
16S-2		5′-TGGCAATCAGCGTCAGGTAATG-3′			
cagA-1	*cagA*	5′-ACCCTAGTCGGTAATGGGTTA-3′	50°C, 60 sec	642–651 (type A)	11
cagA-2		5′-GTAATTGTCTAGTTTCGC-3′		756 (type B)	
				810 (type C)	
				756 (type D)	
VA1-F	*vacA* s1	5′-ATGGAAATACAACAAACACAC-3′	55°C, 30 sec	259	13
VA1-R		5′-CTGCTTGAATGCGCCAAAC-3′			
VA4-F	*vacA* m2	5′-GGAGCCCCAGGAAACATTG-3′	59°C, 60 sec	352	13
VA4-R		5′-CATAACTAGCGCCTTGCAC-3′			

(56/97). And 36.4% (4/11), 56.1% (37/66) and 75.0% (15/20) of our patients who suffered from gastritis, gastric ulcer and duodenal ulcer, respectively, were *H. pylori* positive (Table 1).

The *cagA* genotypes of our *H. pylori*-positive samples were investigated according to standard methods (11). Prevalence of *cagA*$^+$ strains in our *H. pylori*-infected patients was 71.4% (40/56); the *cagA* genotype of *H. pylori* from all the *H. pylori*-infected patients was type A (Table 3). No other genotypes were detected in our patients. The distribution of *cagA*$^+$ strain in patients with gastritis, gastric ulcer and duodenal ulcer was 50% (2/4), 73.0% (27/37) and 73.3% (11/15), respectively (Table 3). Our results showed that Taiwanese patients infected with *cagA*$^+$ *H. pylori* strains were more susceptible to gastric ulcer and duodenal ulcer than were individuals with cagA$^-$ *H. pylori* strains ($p<0.05$, Table 3).

TABLE 3

Prevalence of cagA Genotypes in H. pylori-Infected Patients

Diagnosis	n	*cagA* Type A genotype Positive n (%)	 Negative n (%)	*p**
Gastritis	4	2 (50.0)	2 (50.0)	
Gastric ulcer	37	27 (73.0)	10 (27.0)	<0.05
Duodenal ulcer	15	11 (73.3)	4 (26.7)	
Total	56	40 (71.4)	16 (29.6)	

*χ^2 test with Yates's correction, comparison of the percentage between patients infected with *cagA*$^+$ and *cagA*$^-$ *H. pylori* strains.

The *vacA* genotypes of 56 *H. pylori*-positive samples were investigated as described by Atherton et al. (13). The prevalence of s1 genotype in our patients was 98.2% (55/56; Table 4). And 75% (3/4), 100% (37/37) and 100% (15/15) of our patients who suffered from gastritis, gastric ulcer and duodenal ulcer, respectively, were infected with *H. pylori* strains of *vacA* s1 genotype (Table 4). Our results demonstrated that patients infected with *H. pylori* strain carrying *vacA* s1 genotype were more susceptible to gastritis, gastric ulcer and duodenal ulcer than were individuals with *H. pylori* strains without *vacA* s1 genotype ($p<0.05$, Table 4).

The prevalence of *vacA* m2 genotypes of 56 *H. pylori*-positive samples was subsequently exam-

TABLE 4

Prevalence of vacA s1 and m2 Genotypes in H. pylori-Infected Patients

Diagnosis	n	*vacA* s1 positivity n (%)	*p**	m2 positivity n (%)	*p*†
Gastritis	4	3 (75.0)*		1 (25.0)†	
Gastric ulcer	37	37 (100)*	<0.05	20 (54.1)†	<0.05
Duodenal ulcer	15	15 (100)*		9 (60.0)†	
Total	56	55 (98.2)		30 (53.6)	

*χ^2 test with Yates's correction, comparison of the percentage between patients infected with *vacA* s1 genotype-positive and -negative *H. pylori* strains.

†χ^2 test with Yates's correction, compared with the percentage between patients infected with *vacA* m2 genotype-positive and -negative *H. pylori* strains.

ined. The prevalence of m2 genotype in our patients was 53.6% (30/56; Table 4). And 25.0% (1/4), 54.1% (20/37) and 60.0% (9/15) of our patients who suffered from gastritis, gastric ulcer and duodenal ulcer, respectively, were infected with *H. pylori* strains of *vacA* m2 genotype. Similar to the results regarding *vacA* s1 genotype, patients infected with *H. pylori* strains carrying *vacA* m2 genotype were more susceptible to gastric ulcer and duodenal ulcer than were individuals with *H. pylori* strains without *vacA* m2 genotype ($p<0.05$, Table 4).

We then statistically analyzed the putative correlation between the coexistence of *cagA* and *vacA* s1/m2 genotypes and various *H. pylori*-related gastroduodenal diseases by the Mann-Whitney test. No significant correlation between the coexistence of *cagA* and *vacA* genes with the outcome of *H. pylori*-infection was observed ($p=0.162$, data not shown).

Discussion

Our study demonstrated that the frequency of *H. pylori* infection in a sample of Taiwanese patients with gastroduodenal diseases was 57.7%. The distribution of *cagA*$^+$ *H. pylori* strains in our patients with gastritis, gastric ulcer and duodenal ulcer was 50%, 73.0% and 73.3%, respectively (Table 3). The genotype of all of the *cagA*$^+$ *H. pylori* strains among our patients was type A. There was a discrepancy between our study and previous reports, in which the prevalence of *cagA*$^+$ *H. pylori* strain was as high as 98 – 100% in Taiwan (21, 22). There are two possibilities to explain this discrepancy. First, we investigated *cagA* genotypes directly from gastric biopsy instead of using clinical isolates. It is possible that some *cagA*$^-$ strains were missing due to negative culture results. And second, there might be a difference in the distribution of *H. pylori* strains among different geographical regions in Taiwan. Our results are comparable to the study from mainland China which found that only 68% of *H. pylori* isolates from patients with gastroduodenal diseases were *cagA*$^+$ strain (23). The results of this report indicated that 55.6%, 54.2% and 63.3% of patients who suffered from gastritis, gastric ulcer and gastric cancer, respectively, were *H. pylori*-positive. In terms of the distribution of *cagA* genotypes, Maeda et al. (8) reported that the frequency of type A, type B, type C and type D genotype in Japanese *H. pylori* isolates is 93.5%, 0.12%, 4.5% and 0.64%, respectively. Taken together, these studies suggest that *cagA*$^+$ *H. pylori* with type A genotype may be the most prevalent *H. pylori* strain in eastern Asia.

Regarding the *vacA* gene, 98.2% of our *H. pylori*-positive patients were infected with *vacA*$^+$ *H. pylori* strains. And 75%, 100% and 100% of our patients who suffered from gastritis, gastric ulcer and duodenal ulcer, respectively, were infected with *H. pylori vacA*$^+$ strains carrying s1 genotype (Table 4). This indicated that individuals infected with *H. pylori* carrying *vacA* s1 genotype were especially susceptible to the development of ulcers. In addition, 25%, 54% and 60% of our patients who suffered from gastritis, gastric ulcer and duodenal ulcer, respectively, were infected with *H. pylori vacA*$^+$ strain carrying m2 genotype. This observation indicates that the correlation between *vacA* m2 genotype and peptic ulcer is less significant than that between s1 genotype and peptic ulcer. Wang et al. (21) reported that the s1a genotype (100%) and m2 genotype (87%) of *H. pylori vacA*$^+$ strain were most prevalent in Taiwanese patients with gastroduodenal diseases. Our result of 98.2% prevalence of *vacA* s1 genotype and 53.6% of m2 prevalence was both similar to and significantly different from theirs. This discrepancy reflected our previous hypothesis that the distribution of *H. pylori* strains might differ among the various geographical regions in Taiwan.

No significant difference was discovered between the coexistence of *cagA* and *vacA* genes with the *H. pylori*-infection manifestations (Mann-Whiney test, $p=0.162$, data not shown). Tummuru et al. (24) reported that CagA protein-secreting *cagA*$^+$ *H. pylori* can promote VacA production. However, the authors proposed that the *H. pylori* strain carrying a *cagA* mutant gene could still secrete VacA (25). Moreover, VacA activity can still be detected in some *cagA*$^+$ strains that do not express CagA protein (26). Some studies show that *H. pylori* strains without the ability to produce CagA and VacA cannot induce gastric epithelial cells to secrete IL-8; however, contradictory results have been observed (27, 28). It seems that it is not absolutely necessary for CagA and VacA proteins to coexist for induction of inflammation in gastric epithelial cells.

Summary

Our study leads to the following conclusions: (a) The frequency of *H. pylori* infection in our patients with gastroduodenal diseases was 57.7%. (b) Our data supported previous reports that the pathogenic ability of *cagA*$^+$ *H. pylori* strain was much greater than that of *cagA*$^-$ strains. (c) Type A genotype of *H. pylori cagA* correlated with gastroduodenal diseases. (d) s1 and m2 genotypes of *H. pylori vacA* correlated with development of gastroduodenal diseases, compared to that of *H. pylori* without s1 and m2 genotypes. Above all, although the relationship between *H. pylori* infection and gastroduodenal diseases has been established, the pathogenic factors as well as the host immune responses that dictate the fate of the host still await further investigation, since only some of the infected individuals eventually develop gastroduodenal diseases while others do not.

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Brugada-Like Early Repolarization Pattern Misdiagnosed as Acute Anterior Myocardial Infarction in a Patient with Myocardial Bridging of the Left Anterior Descending Artery

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Abstract

The diagnosis of acute coronary syndrome in patients presenting to the emergency department with chest pain is still challenging. Since the symptoms and electrocardiographic abnormalities of patients with acute myocardial infarction can be indistinguishable from those of patients with other conditions that lead to ST-segment elevation, a high clinical index of suspicion is needed to avoid an incorrect diagnosis and subjecting the patient to unwarranted thrombolytic therapy. Our report concerns a 53-year-old male with myocardial bridging of the left anterior descending artery. He presented with the combined electrocardiographic abnormality of the Brugada-like or early repolarization pattern, which was misdiagnosed as acute anterior myocardial infarction.

Key Words: Brugada-like electrocardiogram, early repolarization, myocardial bridging.

Introduction

THE EVALUATION OF ACUTE CHEST PAIN remains challenging, despite many insights and innovations over the past two decades (1). Since "time is myocardium," it is important to make the diagnosis as quickly as possible. It is equally important, however, not to confuse other causes of ST-segment elevation with acute myocardial infarction (MI) (2, 3). The electrocardiogram (ECG) remains a crucial tool in the identification of acute chest pain with a detailed analysis of patterns of ST-segment elevation (4–6). We present a case and discussion about a patient admitted to the emergency department with chest pain and ECG changes consistent with an acute MI, Brugada syndrome, or early repolarization; the patient subsequently was found to have myocardial bridging (MB).

Case Presentation

A 53-year-old man was admitted to the emergency department with burning, nonexertional chest pain that persisted for 1 hour. The pain had not occurred before and was associated with nausea and vomiting. He was free from any conventional coronary risk factors, including cigarette smoking, diabetes mellitus, hyperlipidemia, hypertension and a family history of coronary artery disease. His medical history was unremarkable, and he was not taking any prescribed medications. He had no family history of sudden death, nor had he experienced any episodes of syncope. At the time of the patient's admission, his temperature was 36.2°C, his pulse was 75 beats per minute, his respiratory rate was 20 breaths per minute, and his blood pressure was 130/85 mm Hg. Auscultation revealed no cardiac murmurs or rales. Upon examination, his other systems were also found to be normal. ECG showed incomplete right bundle branch block (RBBB) with abnormal ST segments in V1–4, consistent with acute anterior MI (Fig. 1). The levels of glucose, urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, troponin T, and the creatine kinase MB

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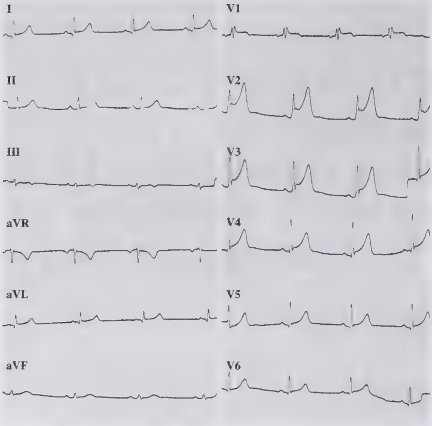

Fig. 1. 12-lead electrocardiogram shows incomplete right bundle branch block with ST-segment (J-point) elevation in leads V1–V4.

isoenzyme were normal (Table). Based on the clinical and electrocardiographic findings, an acute anterior MI was diagnosed, and the patient was treated with an intravenous infusion of streptokinase as a thrombolytic agent. But serial cardiac enzyme values were normal, and his ECG did not evolve as an MI pattern; it remained unchanged. Two days later, his chest pain resolved gradually. Echocardiographic examination revealed no obvious heart diseases, wall motion abnormalities or pericardial effusion.

The patient was referred for coronary angiography and was found to have a significant coronary artery systolic luminal narrowing in the mid segment of the left anterior descending coronary artery at left anterior oblique cranial position (Fig. 2). The right coronary artery and left ventriculogram were normal. Since the patient was free of any personal or family arrhythmic history, a drug challenge test with antiarrhythmic agents was not performed. Beta-blocker therapy was prescribed and the patient was discharged without any problems. At 6-month follow-up, the patient had no cardiac symptoms, and his ECG was unchanged.

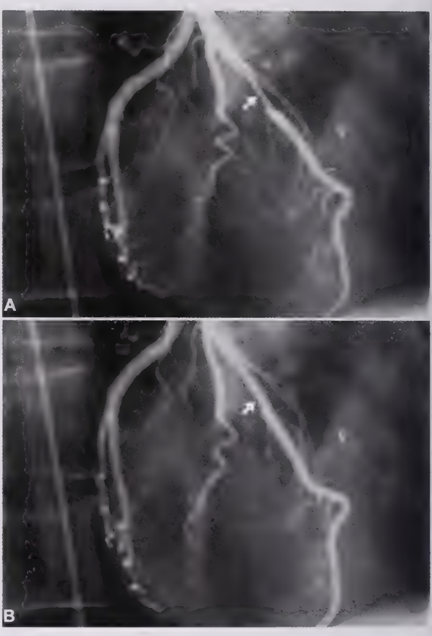

Fig. 2. The coronary angiography shows the myocardial bridging of the left anterior descending artery (arrows) in systole (**A**) and no coronary obstruction in diastole (**B**).

TABLE
Laboratory Data

	On Admission	6 h Later	12 h Later	24 h Later
Glucose (mg/dL)	108	98	100	96
AST (IU/L)	32	32	30	32
CK-MB (IU/L)	10	16	14	14
LDH (IU/L)	274	268	266	270
Troponin t (ng/mL)	<0.01	<0.01	-	<0.01
Total Chol (mg/dL)	-	169	-	-
HDL-Chol (mg/dL)	-	47	-	-
LDL-Chol (mg/dL)	-	90	-	-
Triglyceride (mg/dL)	-	161	-	-

AST=aspartate aminotransferase, CK-MB=creatine kinase MB isoenzyme, LDH=lactate dehydrogenase, Chol=cholesterol.

Discussion

ST elevation is typically seen in acute pericarditis, acute and subacute MI, Prinzmetal angina, old infarction with aneurysm, mirror image of left ventricular systolic overload and normal variants (including early repolarization). It is rarely encountered in hyperkalemia, hypercalcemia, cerebrovascular accidents, hypothermia, pneumothorax and hypertrophic obstructive cardiomyopathy (7). It is well known that the benefit of thrombolytic therapy is greatest when it is given soon after the onset of symptoms of acute ST-segment elevation MI (8). However, the symptoms and electrocardiographic abnormalities of patients with acute myocardial infarction can be indistinguishable from those of patients with other conditions that lead to ST-segment elevation, such as early repolarization, acute pericarditis, hyperkalemia, Brugada syndrome, ventricular aneurysm. Therefore, a high clinical index of suspicion is needed to avoid missing the diagnosis (9), resulting in unwarranted thrombolytic therapy or emergency angiography (2, 3).

"Early repolarization" is a rare normal variant, characterized by a marked, constant elevation of the J point and the ST segment of 2–4 mm, emerging directly from the R wave downstroke, in the anterior precordial leads (accentuated more septally or more laterally) and/or the inferior leads DIII and aVF. The mechanism is not clear (10). Ginzton and Laks studied 19 patients with acute pericarditis and 20 healthy individuals with ST elevation as a normal variant (early repolarization included). They observed that an ST/T ratio of greater than or equal to 0.25 in lead V6 identified the patients with pericarditis and excluded normal variants (11).

Brugada syndrome, first described as a new clinical entity by Pedro and Josep Brugada in 1992, is an inherited cardiac disease causing life-threatening ventricular tachyarrhythmias in individuals with structurally normal hearts and characteristic electrocardiograms showing a pattern of RBBB and ST segment elevation in right precordial leads V1 to V3 (12, 13). Nevertheless, diagnosis and risk stratification are not always clear. The ECG pattern may be dynamic over time and may include transient normalization. In some patients, complete or incomplete RBBB is present. In others, the high-takeoff ST segment mimics the pattern of RBBB, but the wide S waves in leads I, aVL, and V6 that are typically seen in RBBB are missing. The ST-segment elevation is primarily limited to leads V1 and V2 and can have a saddle-back shape, but in typical cases the ST segment begins from the top of the R' wave, is downsloping, and ends with an inverted T wave. This pattern is so distinctive that it should not be mistaken for evidence of acute MI. In anteroseptal MI complicated by RBBB, the downstroke of the R' wave and the beginning of the ST segment have a distinct transition, and the ST segment is horizontal or upsloping, not downsloping (3, 6). In the present case, the electrocardiographic appearance was similar to that seen in Brugada syndrome, but it also resembled early repolarization pattern. But since the patient was asymptomatic for arrhythmic family and personal history, drug challenge was not performed; therefore, the term "Brugada-like" was used.

Acute MI or ischemia from vasospasm involving the right ventricular outflow tract can mimic ST-segment elevation similar to that in Brugada syndrome. This effect is probably the result of a depression of calcium channel current and the activation of ATP-sensitive potassium channel current during ischemia (14). MB causes the systolic compression of a coronary artery by overlying myocardial tissue and usually has a benign prognosis, but in some patients there may be myocardial ischemia, infarction, myocardial stunning, and/or sudden death. Brugada syndromes associated with MB (15) and early repolarization (16) have also been reported in the literature. Significant differences exist between athletes with early repolarization and patients with the Brugada syndrome with regard to the amplitude of ST elevation and QRS duration. The maximum ST elevation is greater in the athletes than in patients with the Brugada syndrome, and Brugada syndrome patients have a longer QRS duration than athletes with early repolarization (16).

The present case is unique in that the combined electrocardiographic abnormality of the Brugada-like and early repolarization pattern coexist with the bridged left anterior descending (LAD) artery. Considering the anamnesis and clinical findings, the condition underlying the ST elevation can be determined in most cases, but, as with this patient, it can sometimes be difficult. It is not clear whether the electrocardiographic appearance of this patient was due to transient ischemia caused by a bridged LAD artery, or if it was due to Brugada syndrome or early repolarization. However, since the ECG remained the same over time, a diagnosis of ischemia related to the bridged LAD artery was unlikely.

In this case report, we presented an interesting ECG sample, but there was no conclusive proof of its etiology. However, this case reminds us that a high clinical index of suspicion is needed to avoid an incorrect diagnosis of acute coronary syndrome.

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Book Reviews

Adult Congenital Heart Disease: A Practical Guide.

Michael A. Gatzoulis, Lorna Swan, Judith Therrien, and George A. Pantely. Malden, MA: Blackwell Publishing; 2005. 228 pp. $54.95. ISBN-0-7279-1668-8.

INTERNISTS AND CARDIOLOGISTS, many of whom are highly skilled in managing adults with an impressive array of serious cardiac problems, are often reluctant to treat an adult patient born with a complex cardiac malformation. If the adult cardiologist has had little or no exposure to the unique anatomy and pathophysiology associated with congenital cardiac malformations, there is little chance that he or she will feel comfortable managing the multitude of problems associated with this condition. The pediatric cardiologist, on the other hand, whose skills are focused on diagnosis and management of complex cardiac malformations, more often than not loses his role as the care provider when the patient becomes an adult and turns to the internist or the adult cardiologist for ongoing cardiac care. A few centers, however, bridge this gap and produce cardiologists fully capable of managing the problems that crop up in adults born with cardiac malformations.

For the internist or cardiologist who needs a guide for the diagnosis and treatment of adult congenital heart disease, there is a new softcover, relatively inexpensive 274-page book that can be particularly helpful. The book, entitled *Adult Congenital Heart Disease: a Practical Guide*, authored by Michael A. Gatzoulis, Lorna Swan, Judith Therrien, and George A. Pantley, is concise and informative. There is a wealth of detail available, more than found in any other "pocket edition" published on this subject to date. Although the print is small, the text is clear enough to help the reader to fully understand the anatomy and pathophysiology of cardiac malformations. In addition, there are informative chapters on various services for adults with congenital heart disease, as well as such complicating factors as pregnancy and contraception; anticoagulation; and lifestyle issues, which are important subjects rarely discussed in standard textbooks.

One illustration, Fig. 13.1, is somewhat misleading. The relationship of the main pulmonary artery to the ascending aorta in congenitally corrected transposition is misrepresented. The illustration shows the ascending aorta medial to the main pulmonary artery, but in fact a hallmark of congenitally corrected transposition is an ascending aorta lateral to the main pulmonary artery. This one error, however, does not significantly detract from the value of this edition. As someone who has spent more than four decades dealing with patients who have congenital heart disease, I would still find it of value to have this volume on my bookshelf.

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Cardiovascular Development and Congenital Malformations.

Michael Artman, D. Woodrow Benson, Deepak Srivastava, and Makoto Nakazawa, editors. Malden, Oxford, Victoria: Blackwell Publishing; 2005. 292 pp. $120.00. ISBN-13: 978-1-4051-3128-5 and ISBN-10: 1-4051-3128-4.

My first exposure to patients with congenital heart disease was in my third year of medical school, in 1952, when I elected to join Dr. Ludwig Eichna's Adult Congenital Heart Disease Clinic at Bellevue Hospital. I attended every Thursday evening throughout my third and fourth year of medical school. It took me a while to realize that the patients at this clinic were highly unusual, since in those days most infants and young children with congenital heart disease did not survive. It was a tribute to the relatively primitive but expert surgery and care provided for these patients that they lived and functioned as well as they did. Of course, aside from the anatomical aspects of their disease, not much was known, and most interventions that we now take for granted did not exist.

The last 50 years have greatly improved the outlook of babies born with congenital heart disease. A major reason for this change is that we are learning more and more about the causes of these defects, and (as has become the rule) investigation of these abnormalities has taught us an enormous amount about the normal embryology of the cardiovascular system. And so the book covers both normal and abnormal cardiovascular development.

Cardiovascular Development and Congenital Malformations, edited by four experts in the field, is a compilation of 70 contributions divided into 13 sections. Each of these contributions, many written by the scientists responsible for the ideas and experiments leading to these advances, is a concise, well-written and well-referenced paper averaging two to four pages in length (although some are longer and more detailed). The brevity of the contributions does not detract from their usefulness, and, if anything, makes them easier to read and understand. Each of the 13 sections (except one) is introduced by an instructive summary of the subject, written by one of the editors.

The first 11 of these sections concern what is known about the developmental biology of cardiovascular embryology. The field is fully covered, including establishment of left-right patterning, cardiogenesis, formation of valves, chambers and conduction tissues, the development of coronary arteries, the role of neural crest cells, formation of outflow tracts and physiological aspects during development. Also included are animal models of congenital cardiovascular malformations and imaging techniques in embryos. The last two sections of the volume are more clinically oriented and deal with patent ductus and human clinical genetics and epidemiology as they concern congenital heart disease. While one could highlight many of the individual contributions, I was particularly impressed by two papers (provided by Bruce Gelb), which typify the new molecular approaches to an understanding of these complex disorders, and an impressive set of contributions concerning various aspects of animal models of DiGeorge syndrome. There are numerous illustrations and a truly wonderful collection of color plates that illustrate many of the points made in the papers.

The book is quite easy to read, and each of the contributions provides a comprehensive bibliography for those who wish to delve more deeply into the subject. If I were to find one thing to quibble about, it is that many of the bibliographies end in 2001, with some going to 2002 and rarely into 2003. However, by using PubMed, one can probably update these bibliographies, something that hopefully will be done in a future edition. That such an update of the field is already necessary is shown by the acknowledgments by the various authors as to what is not yet known. This comprehensive collection should be of great interest to all pediatric cardiologists, embryologists and practitioners of fetal medicine and belongs on their shelves for ready reference.

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The Brugada Syndrome: From Bench to Bedside.

Charles Antzelevitch, Pedro Brugada, Josep Brugada, and Ramon Brugada, editors.
Malden, MA: Blackwell Publishing; 2005.
248 pp. $99.50. ISBN-1405127783.

First described as a clinical entity in 1992, the Brugada syndrome has since attracted great attention from the medical community because of its association with a high risk for sudden death in young adults, particularly men. The Brugada syndrome is characterized by ST segment eleveation in the right precordial EKG leads in patients with structurally normal hearts. The syndrome is believed to be responsible for 4 – 12% of all sudden deaths and at least 20% of deaths in patients with structurally normal hearts. Investigation into the etiology of the Brugada syndrome has revealed that it is characterized by an abnormality in phase 2 of the action potential, leading to fatal ventricular arrhythmias. Although the etiology remains controversial, several risk factors have been identified for a Brugada-type EKG and the associated ventricular arrhythmias and sudden death.

In *The Brugada Syndrome: From Bench to Bedside*, edited by Charles Antzelevitch, the authors comprehensively describe the many aspects of Brugada syndrome. The book begins with an overview of the clinical characteristics, definition, mechanism, and therapy of the disease by Dr. Antzelevitch, the lead author of the current consensus statement for the management of patients with the syndrome. From there, after a brief description of the history of Brugada syndrome, we get an in-depth review of the genetics of the syndrome, the make-up and mutations of the sodium channel attributed to the syndrome, and the underlying cellular mechanisms believed to underlie the arrhythmic manifestations. The book then moves into more clinical aspects of the disorder. The diagnostic criteria are described with distinguishing characteristics relative to other disorders linked with sudden death. The role of genetics in clinical practice is reviewed, including the gender differences inherent to the disorder. Finally, the issue of prognosis and risk stratification of individuals with the Brugada EKG is examined, with recommendations for deciding who should be treated with an implantable cardioverter defibrillator.

In summary, *The Brugada Syndrome: From Bench to Bedside* is a comprehensive review of all aspects of the syndrome, although little attention is paid to the ongoing controversies on the role of electrophysiologic testing for risk stratification. It is an excellent read not only for cardiologists and electrophysiologists but also for those interested in how to approach a disorder comprehensively, through molecular, genetic, and clinical aspects. Indeed, the methodology used to explore the features of Brugada syndrome in this book could serve as a paradigm for the approach to various clinical syndromes in medicine.

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Textbook of Hemophilia.

Christine A. Lee, Erik E. Berntorp, and
W. Keith Hoots, editors. Malden, MA:
Blackwell Publishing; 2005. 416 pp. $199.00.
ISBN-1-405-12769-4.

Hemophilia and the related bleeding disorders have been the subject of numerous monographs. This text is a compilation of 63 chapters written by 90 world authorities. Topics covered include the basic mechanisms of hemostasis, biochemistry of clotting factors, relevant genetics, and current and evolving treatments (specifically, gene therapy).

The book also contains an up-to-date presentation of the basic science of hemophilia, the clinical and laboratory evaluation of patients, the therapies, and the pharmacoeconomics of treatment. There is an appropriate mix of the basic science of hemophilia A and B (factor IX and VIII deficiency, respectively) with information on the different factor products available for treatment. Development of auto-antibodies or inhibitors, a major complication to treatment, is clearly described. Other complications are chronic joint disease due to recurrent joint bleeding and potential exposure to infectious agents in factor preparations. All these problems are discussed, as well as the care of the bleeding infant/child and obstetrical/gynecologic patients.

Although the bulk of the text is devoted to hemophilia A and B, any text worth its salt must include chapters on von Willebrand disease and the rare bleeding disorders (factors II, V, XI etc.)—and this one does.

The writing style is straightforward and the tables and illustrations (black and white) are good companions to the text. For those not familiar with hemophilia treatment options, a foldout with explicit treatment guidelines would have been a nice touch.

Overall, this is a concise (each chapter ranges from 4–6 pages) but thorough treatment of bleeding disorders. Certainly a worthwhile monograph for hematologists, surgeons, gynecologists, and dentists.

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Clinical Obesity in Adults and Children.

Peter G. Kopelman, Ian D. Caterson, and
William H. Dietz, editors. 2nd edition.
Malden, MA: Blackwell Publishing; 2005.
493 pp. $199.95. ISBN-10:1-4051-1672-2,
ISBN-13: 978-1-4051-1672-5.

The epidemic of obesity in Western societies has stimulated considerable research on the effects of obesity on public health. One major example: It is estimated that over 800,000 residents of New York City have diabetes, with the vast majority having type 2 diabetes, associated with obesity. Multidisciplinary approaches are necessary to tackle this emerging epidemic, which is now afflicting tens of thousands of children in New York City alone.

This book is comprehensive and easy to read. There are three distinct sections: epidemiology, associated morbidities and management. All are well written and current. Of particular interest to the general practitioner are the chapters dealing with management. Often clinicians experience great frustration when trying to persuade their patients to modify their behavior. The section on the management of obesity provides realistic data that I believe can help us with this challenge.

The book also considers the social consequences of obesity and the differences between cultures in how they deal with obesity.

Proper emphasis is placed on the medical evaluation of the obese patient as well as the important co-morbidities of sleep apnea, hypertension and dyslipidemia. The message is clear—evaluate your patient for the consequences of obesity and treat these syndromes by treating the obesity. This book could serve as an excellent resource to educate patients about the potential risks of obesity. I would also recommend it highly to clinician nurse specialists.

Overall, this excellent review is evidence-based and user friendly.

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Letters to the Editor

To the Editor:

In reporting a rare consequence of cervical manipulation, the article about chiropractic sympathectomy, by AM Khan et al. (1), should be of interest to all health care providers whose scope of practice includes spinal manipulative therapy (SMT). Since there is increasing utilization of SMT by medical doctors and physical therapists (2), no profession is immune to the sequelae of a manipulative procedure (3, 4).

We agree that health care providers should be aware of the potential adverse reactions associated with an intervention. However, it is unreasonable to recommend premanipulative neuroimaging for all neck pain patients as a screen for patients at risk of subsequent arterial dissection. The authors appear unaware of the relevant studies, including imaging of the neck arteries of patients with known dissections and stroke, which conclude that there do not appear to be clinical, laboratory or imaging studies which conclusively demonstrate any predisposition to arterial dissection from cervical SMT (2, 5). We hope that interdisciplinary clinical and pathological studies may provide clearer direction in this regard.

Finally, to title this article "Chiropractic Sympathectomy" is incorrect pathologically, especially in consideration of the patient's reported full recovery. As noted, the patient suffered an oculosympathetic palsy that appeared to be temporally associated with a cervical manipulation. Surely, patients' and practitioners' interests are better served when authors of scientific and professional articles restrict themselves to being factual and accurate, leaving sensationalism and conjecture to the tabloids.

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Authors' reply:

Thank you for your interest in our article.

We agree that no profession is immune to sequelae of a manipulative procedure but must emphasize that all should be aware of potential complications to spinal manipulative therapy (SMT) (1–5). We are also aware that there is no screening imaging of choice to alert the health care profession to potential cases of arterial dissection. However, we don't agree that there are no clinical, laboratory or other warning signs. We would like to point out some of these risk factors, e.g., hereditary connective tissue disorders such as Ehlers Danlos syndrome (EDS), genetic diseases (MTHFR), familial and seasonal patterns, infections, homocysteinemia, and fibromuscular dysplasia (6–19). High-risk groups should be identified and further testing with imaging modalities should be done if deemed necessary (20–22).

Drs. Steiman and Mior imply that we were unaware of a number of studies (e.g., Haldeman et al., J Neurology 2002; 249:1098–1104 and Smith et al., Neurology 2003; 60:1424-1428) "which conclude that there do not appear to be clinical, laboratory or imaging studies which conclusively demonstrate any predisposition to arterial dissection from cervical SMT." We would like to point out that both of these works were retrospective studies that showed that cervical SMT preceded the occurrence of stroke and cerebral artery dissection in a significant number of patients. Neither study addressed the issue raised as to whether pre-SMT neuro-imaging might reduce the occurrence of neurological sequelae in patients with neck pain. Until this point is resolved, we continue to believe that neuro-imaging is clinically and medicolegally prudent prior for SMT for patients with neck pain.

Drs. Steiman and Mior also question the use of the term "chiropractic sympathectomy," since it is "incorrect pathologically" for a patient in whom the symptoms were reversible. On this point, we also disagree. There are other instances where the term "sympathectomy" is employed when the condition is not permanent. For example, "chemical sympathectomy" is a procedure used to treat reflex sympathetic dystrophy despite the recognition that its effects are transient. Thus, far from representing "sensationalism" and "tabloid" journalism, we believe that the term we chose for this article is appropriate and based on established medical precedents.

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To the Editor:

I am a medical doctor studying in Turkey. My speciality is obstetrics and gynecology. While preparing an article about fetal growth restriction and metabolic syndrome, I found an article in *The Mount Sinai Journal of Medicine* (vol. 72 no. 4 July 2005) titled "The Metabolic Syndrome and Cardiovascular Disease." In the article, the WHO criterion for microalbuminuria is given as an albumin excretion rate of "≥ 20 mg/min." I think the milligram terminology should be micrograms. Aside from this, the article was quite excellent, because the pathophysiology was described so clearly.

I look forward to reading future articles in the *Journal*.

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Author's reply:

The albumin excretion rate used by WHO in the definition of metabolic syndrome is indeed greater than or equal to 20 micrograms/min, as outlined in a 1999 report (1). Furthermore, a subsequent WHO report discouraged the use of the term "microalbuminuria" in favor of the phrase "abnormal albumin excretion rate" (2).

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1. http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf (accessed 12/13/05)
2. http://whqlibdoc.who.int/hq/2002/9241590483.pdf (accessed 12/13/05)

To the Editor:

Organophosphate poisoning (OPP), acute and chronic, still remains an underrecognized medical health problem across the world. Sebe and colleagues, in a recent article (1), report a pregnant woman with fetal death after ingestion of chlorpyrifos, a situation that is even more neglected in toxicology. The apparent 'better' outcome of the woman in the case study who noticed loss of fetal movements within two hours of ingestion, makes one speculate whether the diffusion of chlorpyrifos was diverted towards the fetal circulation. And, if so, do pregnant women with acute OPP need a different regime or different formulation for cholinesterase reactivation with oxime?

Chlorpyrifos is extremely lipophilic, and equilibration between maternal and fetal blood may occur in a matter of hours. U.S. studies on indoor pesticide use and prenatal exposure have shown a significant inverse relationship between birth weight and length (a decrease in birth weight by 42.6 gm and in birth length by 0.24 cm) with each log unit rise in plasma chlorpyrifos levels (2). A recent study has shown that chlorpyrifos is teratogenic and embryotoxic in mice at doses below those that cause significant maternal toxicity (3). Chlorpyrifos is bioactivated by cytochrome P450-dependent desulfuration (CYP2D6 isoform) in the liver to chlorpyrifos-oxon. Studies using quinine as a specific inhibitor of CYP2D6 have shown that individual polymorphisms of CYP2D6 can influence organophosphate toxicity (4). CYP2D6 expression has been detected in fetal liver, and 3–10% of Caucasians are poor metabolizers due to inheritance of 2 defective CYP2D6 alleles. Fetal hepatic drug conjugation may prolong fetal exposure to metabolites, and if the drug is excreted in fetal urine, it can be recycled via amniotic fluid and fetal swallowing which may prove to be lethal.

Reactivation of inhibited acetylcholinesterase (AChE) by nucleophilic displacement of the OP moiety from the active-site serine of the inhibited enzyme is the primary mechanism of action of oximes. The rate of this action varies with the structure of the bound organophosphate and the oxime involved. In our study involving acute OPP in South India, we showed that persistent inhibition of butyrylcholinesterase may be the underlying cause of lack of oxime efficacy, and that timing of oxime therapy may be the key to reversing acute OPP toxicity (5). Interestingly, quaternary ligands such as edrophonium and decamethonium have been shown to accelerate the reactivation by oximes by a maximum of 12.0-fold and 3.0-fold respectively, which certainly appears promising (6). The use of such quaternary ligands complexed with oximes may prove to be future therapeutic strategies and merits further study.

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Abstracts

The following abstracts were presented by investigators at the Twenty-First Annual Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine Research Evening on June 8, 2005. Most of the investigators serve in the Samuel Bronfman Department of Medicine, including those working at affiliated institutions such as the Bronx Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Elmhurst, NY; Queens Hospital Center, Jamaica, NY; and St. Joseph's Hospital and Medical Center, Paterson, NJ. Abstracts from Queens Hospital Center and Jersey City Medical Center were presented as posters on Research Day, held on May 11, 2005 and May 25, 2005, respectively.

Research in Medicine 2005
Mount Sinai School of Medicine

Basic Science Research

CD44 Is a Physiological Ligand for E-Selectin on Neutrophils. J. Chang, Y. Katayama, A. Hidalgo, A. Peired, and P.S. Frenette. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Selectins and their glycoconjugated ligands are essential for blood neutrophil (PMN) extravasation into inflammatory and infectious sites. However, the identity and contribution of physiological E-selectin ligands (ESLs) on PMNs is largely unknown. This knowledge gap, despite intense research effort, originates in part from the unavailability of inhibitory antibodies, due to the poor immunogenicity of highly glycosylated and conserved ESL epitopes. Mice deficient in P-selectin glycoprotein ligand-1 (PSGL-1), a ligand for all three selectins, exhibit some deficits in E-selectin-mediated rolling but PSGL-1 appears dispensable for E-selectin-mediated PMN extravasation, suggesting a role for other ESLs. A glycoform of CD44 specific to immature progenitor cells was shown to bind to E-selectin *in vitro*. To assess whether CD44 derived from mature myeloid cells could interact with E-selectin, we extracted CD44 from G-CSF-differentiated 32D cells and from mouse PMNs. Immobilized CD44 bound to soluble E-selectin through sialylated, α1,3-fucosylated, N-linked glycans. Intravital microscopy analyses of mice deficient in CD44, PSGL-1 or both, revealed that CD44 mediated slow leukocyte rolling on E-selectin in cremaster venules. PMN extravasation in doubly deficient mice, but not either singly deficient mice, was significantly reduced in thioglycollate-induced peritonitis (by 44%, p=0.005) or in skin pouches instilled with staphylococcal enterotoxin A (by 77%, p=0.006), suggesting that CD44 cooperates with PSGL-1 in mediating E-selectin-dependent PMN extravasation. We also report that CD44 expressed on human neutrophils can bind specifically to E-selectin. Interestingly, neutrophil CD44 purified from a patient with leukocyte adhesion deficiency type II (LADII; which lack selectin ligands) failed to bind E-selectin, but binding of CD44 could be fully restored by incubation of LADII PMNs with α1,3-fucosyltransferase VI and GDP-fucose. Thus, our results demonstrate that CD44 is a physiological ligand for E-selectin on mature mouse and human neutrophils.

The study was supported by a training grant from the National Institutes of Health T32 DK07792 (J.C), a Fellowship from National Blood Foundation (A.H.), and R01 grants DK56638 and HL69438 (P.S.F).

Evidence for Increased Neointima Formation in Podocan Knockout Mice compared to C57/BL6 Wild Type Mice after Arterial Denudating Injury. R. Hutter*, L. Huang*, C. Valdiviezo, J.J. Badimon, and P. Klotman. *Both authors contributed equally to this study. Mount Sinai School of Medicine, New York, NY.

Background: Acute arterial lesion formation is determined by migratory and proliferative cellular events. An important group of extra-cellular matrix proteins is characterized by small leucin-rich repeat (SLR) sequences and can act as key regulator of cell growth in renal and vascular disease. Podocan is a novel member of the SLR protein family and recently has been shown to be expressed in vascular smooth muscle cells inhibiting cell proliferation *in vitro*. Therefore, we hypothesized that if podocan indeed controls cell growth also *in vivo* mice deficient in podocan might exhibit an increased proliferative response to vascular injury.

Methods: Using a mouse model of arterial injury we examined the effects of podocan genotype on neointimal area and cellularity as well as on the outer arterial wall response to injury. C57/BL6 wild type (WT) mice (n=10) and syngeneic C57/BL6 mice either hetero- (n=15) or homozygous (n=15) for the podocan knockout genotype underwent femoral arterial denudation and were sacrificed at 4 weeks for histopathologic analysis of the injured femoral arterial segment.

Results: Mice homozygous for the podocan knockout genotype showed a dramatic and significant increase in neointima area at 4 weeks after arterial injury compared to WT mice (11.6 ± 1.8 vs. 4.4 ± 1.3 × 10^{-3} mm^2, *P*<0.01). Interestingly, medial area and overall arterial size were not different between the two groups (14.5 ± 0.8 vs. 14.8 ± 2.0 × 10^{-3} mm^2, *P*=NS, and 50.5 ± 15.0 vs. 53.6 ± 14.0 × 10^{-3} mm^2, *P*=NS, respectively). Consistently, neointima to media ratio was also strongly increased in podocan knockout mice (0.82 ± 0.12 vs. 0.33 ± 0.10, *P*<0.01). Neointimal cell density per mm^2 did not show a significant difference between podocan knockout and WT mice reflecting increased synthesis of extracellular matrix material by proliferating cells. When comparing mice heterozygous for the podocan knockout genotype to WT mice a similar pattern and trend of data was observed, however it was less pronounced and did not reach the level of statistical significance.

Conclusions: This study represents the first *in vivo* evidence that podocan as a novel member of the SLR protein family is implicated in the regulation of the arterial response to injury process. Mice homozygous for the podocan knockout genotype with complete deficiency in the podocan gene product showed a strong and selective increase in neointima formation with no significant effect on the outer arterial wall architecture. This observation points to a possible specific growth inhibitory/controlling effect of podocan on highly activated intimal smooth muscle cells. However, further studies are necessary to determine the mechanism of podocan-mediated regulation of neointimal growth and to discriminate between local and systemic effects of the podocan knockout genotype.

VEGF Is a Critical Regulator of Reendothelialization and Neointima Formation in a Mouse Model of Arterial Injury. R. Hutter, F. Carrick, C. Valdiviezo, C. Wolinsky, J. Rudge, S. Wiegand, V. Fuster, J.J. Badimon, and B.V. Sauter. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Background: Luminal endothelial integrity and rate of re-endothelialization are critical factors in the formation of neointima after arterial injury. VEGF, a potent endothelial mitogen, has been advocated for treating post-angioplasty intimal hyperplasia. A soluble, chimeric VEGF-receptor (VEGF-Trap) has been shown to inhibit endothelial cell proliferation and angiogenesis. To determine the role of VEGF in arterial repair we overexpressed both VEGF and VEGF-Trap in a mouse model of arterial injury.

Methods: Four groups of C57/BL6 mice underwent denudating endothelial injury one day after *systemic* injection of recombinant adenovirus expressing (1) VEGF, (2) VEGF-Trap, (3) VEGF plus VEGF-Trap, or (4) control adenovirus.

Results: Circulating transgene levels were significantly elevated 2 and 4 weeks after gene delivery and arterial injury. VEGF treatment significantly accelerated reendothelialization and luminal endothelial cell proliferation as measured by the expression of endothelial Ki-67 (76% ± 8 vs. 60% ±13; $P<0.05$, and 35% ± 9 vs. 2.3% ± 0.7; $P<0.01$ respectively). This accelerated endothelial repair subsequently resulted in decreased neointima area compared to controls (2.5 ± 1.5 vs. $7.5 \pm 2.6 \times 10^{-3}$ mm^2, $P<0.01$). Co-treatment with VEGF and VEGF-Trap eliminated circulating VEGF and completely abrogated the beneficial effect of VEGF on reendothelialization and neointima formation. Interestingly, selective removal of *endogenous* VEGF by VEGF-Trap overexpression alone also led to strong inhibition of reendothelialization at 2 weeks (25% ± 4.8 vs. 60% ± 12.6, $P<0.01$) and increased neointima formation at 4 weeks (17.3 ± 7 vs. $7.5 \pm 2.6 \times 10^{-3}$ mm^3, $P<0.01$) compared to controls.

Conclusions: VEGF overexpression accelerated endothelial repair and inhibited neointima formation after arterial injury. Conversely, sequestration of exogenous and/or *endogenous* VEGF by VEGF-Trap inhibited re-endothelialization and dramatically increased neointima size. This emphasizes not only the therapeutic potential of VEGF but also the critical role of physiological VEGF levels and the VEGF pathway in vascular repair *via* maintenance of luminal endothelial integrity.

Focal Adhesion Kinase (FAK) Abnormalities in Autosomal Recessive Polycystic Kidney Disease (ARPKD). S. Israeli, K. Amsler, and P.D. Wilson. Department of Medicine, Division of Nephrology, Mount Sinai School of Medicine, New York, NY.

Autosomal Recessive Polycystic Kidney Disease (ARPKD) occurs in 1:20,000 live births. It is characterized by abnormal proliferation of renal epithelial collecting tubule cells, substantial cyst formation and early death (Wilson PD, NEJM 2004; 350:151 – 164). Mutations in the PKHD1 gene, encoding fibrocystin, cause ARPKD (Ward CJ, et al. Nat Genet 2002; 30:259269). Another form of polycystic kidney disease, Autosomal Dominant Polycystic Kidney Disease (ADPKD), is also characterized by cystic dilation of renal tubules. Renal epithelial cells derived from ADPKD kidneys demonstrate increased extracellular matrix (ECM) adhesion and decreased migration when compared to normal, age-matched, adult human collecting tubule cells.

Correct focal adhesion complex assembly is essential for many cellular functions including ECM attachment, spreading and migration. Binding of cell surface receptors (integrins) to ECM activates integrin clustering and formation of the intracellular focal adhesion complex. Proteins in the focal adhesion complex include focal adhesion kinase (FAK), paxillin, p130CAS, src kinases, talin, vinculin and tensin. Once recruited and activated by phosphorylation at the focal adhesion, the associated focal adhesion proteins recruit and organize actin bundle filaments, further strengthening the focal adhesion complex, increasing cell tension on the ECM, and providing new attachment sites for cell adhesion and motility. Loss of FAK from the focal adhesion complex has been observed in ADPKD cyst lining epithelia (Wilson et al., Lab Invest 1999; 79:1311 – 1323), suggesting that disruption of downstream signaling events from the focal adhesion impact on the adhesion and motility defects in ADPKD. While the loss of focal adhesion integrity has been established in ADPKD, less is known about focal adhesion complex assembly and downstream signaling in ARPKD.

Preliminary studies have shown increased adhesion to type I collagen and decreased migration in response to growth factor gradient of ARPKD renal collecting duct epithelial cells by comparison to age matched normal human fetal collecting tubule (HFCT) epithelia *in vitro*. Since FAK phosphorylation on tyrosine 397 has been shown to regulate cell adhesion to ECM, PY397- FAK levels were examined in adherent ARPKD versus HFCT cells, as well as total FAK protein content. Both total FAK and FAK tyrosine397 phosphorylation were decreased in ARPKD cells in adherent cells in a time-dependent manner (2 – 48 hours). Further studies are in progress to determine whether phosphorylation of FAK at other tyrosine and/or serine sites are also altered in ARPKD. Our studies to date, thus show some interesting similarities in adhesion, migration and FAK-phosphorylation defects in ARPKD and ADPKD.

Effect of Chinese Herbal Formulas on T Cell Responses in Patients with Peanut Allergy or Asthma. J. Ko, P.J. Busse, L.P. Shek, S. Noone, H.A. Sampson, and X. Li. Pediatric Allergy and Immunology, Mount Sinai School of Medicine, New York, NY.

Rationale: We previously reported that the "anti-allergy" Chinese herbal formulas ASHMI and FAHF-2 are effective in treating asthma and peanut allergy and in suppressing Th2 responses in murine models. We sought to examine the effect of these two herbal formulas on T-cell responses of patients with allergic asthma or peanut allergy.

Methods: Eight patients with peanut allergy and asthma and six with peanut allergy alone were studied. Peripheral blood mononuclear cells were isolated and cultured with crude peanut extract (CPE, 200 μg/ml) with and without herbal formulas (ASHMI for asthmatic patients or FAHF-2 for peanut-allergic patients, 50 μg/mL). Proliferative responses and cytokine production were determined by thymidine incorporation and ELISA respectively.

Results: Twelve patients with peanut allergy and asthma were studied. Peripheral blood mononuclear cells were isolated and cultured with crude peanut extract (CPE, 200 μg/mL) with and without herbal formulas (ASHMI or FAHF-2, 50 μg/mL). Proliferative responses and cytokine production were determined by thymidine incorporation and ELISA respectively. For ASHMI, mean thymidine incorporation increased from 500 to 6752 cpm following CPE stimulation and decreased to 5395 cpm with addition of ASHMI. Mean IL-5 production (pg/mL) increased from 77 to 455 following CPE stimulation, decreasing to 212 with ASHMI treatment ($p<0.05$). Mean IL-13 production (pg/mL) was increased from 1003 to 2564 by CPE, decreasing to 1554 with ASHMI treatment ($p<0.05$). IL-4 production was undetectable in all samples. Mean IFN-γ production (pg/mL) was not suppressed with ASHMI treatment: 55 with medium alone, 707 with peanut extract, and 1098 with ASHMI. T-cell proliferation and cytokine results from peanut allergic patients using FAHF-2 were similar. Cell viabilities in antigen alone and antigen herbal formula-treated cells were not different.

Conclusions: ASHMI and FAHF-2 down-regulated Th2 responses, suggesting that they may have potential benefit to patients with food allergy and asthma.

KLF6 Tumor Suppressor Has Critical Roles in Vascular, Hematopoietic and Placental Development. N. Matsumoto. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Background: KLF6 is a ubiquitously expressed Krüppel-like zinc finger transcription factor identified as a tumor suppressor gene in prostate cancer, colorectal and hepatocellular carcinomas (Tal-Kremer et al., AASLD 2002 #924). *KLF6* is also an immediate early gene that is rapidly upregulated in hepatocytes following partial hepatectomy and in hepatic stellate cells after injury. Its expression is regulated in a tissue-restricted manner during development (Laub et al., Mech Dev 2001). These broad activities yet defined sites of expression suggest a potentially important role of *KLF6* in development. We previously reported the impaired ability of *KLF6*$^{-/-}$ ES cells to differentiate into 3 germ layers, resulting in loss of differentiation into an hepatic lineage *in vitro* (Matsumoto et al., AASLD 2003 #267).

The **aim** of this study was to examine the role of KLF6 in mouse embryogenesis.

Materials and Methods: *KLF6*$^{+/-}$ ES cells were generated by homologous recombination through selection with a *KLF6* targeting vector containing the neomycin/lac Z cassette. Chimeric mice were produced by microinjection of targeted ES cell clones into C57BL6 blastocysts, then transferred to pseudopregnant mothers. Chimeric males were mated with C57BL6 females and germline transmission of the mutated allele was verified by Southern blot and PCR analysis of tail DNA from F1 offspring, using two primer pairs amplifying *KLF6* exon2 and neo sequences respectively. Two lines of *KLF6*$^{+/-}$ mice were obtained and analyzed.

Results: No viable *KLF6*$^{-/-}$ mice were recovered among > 300 offspring, and the number of *KLF6*$^{+/-}$ mice was ~ 35% less than expected, indicating complete lethality of the *KLF6*$^{-/-}$ phenotype and partial lethality of the *KLF6*$^{+/-}$ phenotype. *KLF6*$^{-/-}$ embryos die between E10.5 to E12.5 and are much smaller, paler, and atretic compared to *KLF6*$^{+/+}$ and *KLF6*$^{+/-}$ embryos. Although *KLF6*$^{-/-}$ embryos had a beating heart at E10.5, vascularization and hematopoietic colony formation assay of *KLF6*$^{-/-}$ yolk sacs were severely impaired, suggesting combined defects in vascular development and hematopoiesis. This phenotype implicates a defect in hemangioblasts, thought to be a precursor of both vascular and hematopoietic tissues. The findings correlate entirely with defects observed during differentiation of $KLF6^{-/-}$ ES cells (Matsumoto, AASLD 2003 #267). In addition, genetic crosses between $KLF6^{+/+}$ and $KLF6^{+/-}$ mice revealed that frequent embryonal deaths in $KLF6^{+/-}$ mice occurred only when the genotype of the maternal but not paternal mouse was $KLF6^{+/-}$. Since KLF6 is strongly expressed in placenta, this suggests that some maternal factor regulated by KLF6 may be critical for placentogenesis, which might lead to embryonic deaths of $KLF6^{+/-}$ and possibly $KLF6^{-/-}$ mice.

In **conclusion**, these data indicate a broad contribution of *KLF6* to mouse development, with specific roles in morphogenesis, vasculogenesis, hematopoiesis and placentogenesis.

MMTV-like Particles in Human Breast Cancer. S.M. Melana, J-D Jiang, S. Dales, J.F. Holland, and B.G.T. Pogo. Mount Sinai School of Medicine, New York, NY, and the Rockefeller University, New York, NY.

We have previously reported sequences homologous to the env gene of mouse mammary tumor virus (MMTV) but not to the human endogenous retrovirus in 38% of the 314 human breast cancers studied (Wang et al., Cancer Research 1995; 55:5173). The sequences were absent from other human and tissues and they were expressed in most of the positive breast specimens (Wang et al., Cl. Cancer Research 1998; 4:2565). The complete 9.9 Kb proviral sequence of an MMTV-like agent has been amplified and sequenced in two breast cancers (Liu B, et al. Cancer Res 2001; 61:1754–1759). Structural features of this provirus suggest that it is functional. We have now looked for the presence of viral particles and viral genes in primary cultures of env sequence positive tumors. Retroviral particles budding from cells and in particulate fractions from culture media were observed by electron microscopy. Particulate fractions also shown reverse transcriptase (RT) activity and the presence of all viral genes as detected by RT-PCR. The RT activity peaked at densities characteristic of retroviruses in sucrose gradients. None of these properties were observed in similar studies with putatively normal breast primary cultures. Taken together, these findings support the identification of a human mammary tumor virus (HMTV) similar to MMTV. Co-cultivation experiments of virus-producing and normal mammary epithelial cells demonstrated transfer of viral sequences and expression of env proteins suggesting infectivity.

Human Alpha Defensin1 Inhibits Influenza Virus Replication by Preventing a PKC-Mediated Entry Event. M. Salvatore. Mount Sinai School of Medicine, New York, NY.

Introduction: Activation of the innate immunity is the first line of defence of the body against viral infection. In the recent years the complex relationship between the activation of type1 interferon system and influenza virus has been extensively studied. Other less studied effectors of the innate immunity are likely to play a role in modulating the body response to viral infection. Alpha-defensins are small, widely distributed antimicrobial peptides present in neutrophil granules that are active against many bacteria, fungi and HIV. It is becoming increasingly clear that defensins play an important role both as effectors of innate immunity and as modulators of adaptive immunity. While their antibacterial activity is attributed to the disruption of cell membranes, their mechanism of action and spectrum of activity against viruses other than HIV is still unclear. We studied the anti-influenza virus activity as well as a mechanism(s) of inhibition α-defensin-1.

Methods: Recombinant human α-defensin-1 (HNP1) was obtained from Cell Sciences. Influenza A/WSN/33 virus strain was used to infect MDBK cells (MOI=0.001); titers were measured by plaque assay. For viral protein expression studies, infected cells (MOI=5) were labeled at various intervals with ^{35}SCys-Met. CytoTox 96® assay (Promega) was used to measure cytotoxicity. Activated protein kinase C (PKC) was detected by western blot.

Results: Influenza virus replication was inhibited when virus was pre-incubated with HNP1 (25 µg/mL) and the inhibitor was present during and after infection ($<10^2$ vs. $6\text{x}10^6$). More importantly, similar inhibitory effect on viral replication was observed when HNP1 was added only after infection ($1.7\text{x}10^7$ vs. $6\text{x}10^6$). In contrast, no effect of HNP1 on virus replication was observed when the substance was only present during pre-incubation of virus before infection followed by wash-off and no add-back suggesting that HNP1 blocks influenza virus replication following entry events. The effect of HNP1 was dose-dependent. Time course labeling of protein expression in infected cells treated with HNP1 showed decreased synthesis of viral (but not cellular) proteins. To ensure that the antiviral effect was not due to general cytotoxicity, cell viability was measured. Treatment of uninfected cells with 10 or 20 µg/mL of HNP1 was not associated with cytotoxicity. HNP1 also prevented cytotoxicity by WSN infection in a dose-dependent fashion. HNP1 did not inhibit influenza virus replication in the minireplicon system where the entry events are not necessary for viral infection supporting a block of early event. HNP1 down regulated PKC activation by WSN as demonstrated by a decrease in phosphorylated PKC in HNP1 treated cells.

Conclusions: Our data show that α-defensin-1 inhibits influenza virus replication following viral entry. The inhibition is dose and time dependent and it is not due to general cytotoxicity. α-defensin-1 inhibits phosphorylation of PKC which is known to play a role in influenza infection. Since PKC activation is necessary for influenza trafficking in endosomes, HNP1 may block late entry events and inhibit influenza virus replication possibly by inhibiting PKC. The identification of novel effectors of the immune response against influenza virus will provides a better understanding of the host-pathogen interactions and present new strategies for prevention and therapy.

Significantly Decreased Expression of the Tumor Suppressor KLF6 in 85% of HCCs Contributes to Enhanced Growth and Reduced Differentiation. S. Kremer-Tal, G. Narla, M. Banck, A.V. Difeo, J-S Lee, E. Zimran, S.S Thorgeirsson, J.A Martignetti, and S.L Friedman. Division of Liver Diseases and Department of Human Genetics, Mount Sinai School of Medicine, New York, NY, Ben Gurion Medical School, Beer-Sheva, Israel and Center for Cancer Research, National Cancer Institute, National Institute of Health, Bethesda, MD.

KLF6 is a tumor suppressor gene inactivated in a growing number of tumors, including prostate, colon, glioma, lung, head and neck, as well as HCC, suggesting a generalized role in cancer pathogenesis. We have previously established its role in normal hepatocyte growth, whereas it is functionally inactivated in the majority of HCCs by deletion and/or inactivating mutation.

The **aim** of this study was to determine whether KLF6 expression is decreased in HCC compared to normal livers, and to characterize its effects on cell growth and differentiation in HCC cell lines.

Methods: KLF6 mRNA levels were quantitated in HCC samples from 39 patients and 10 normal livers by QRT real-time PCR. HepG2 cells stably expressing KLF6 were established by retroviral infection. Growth was assessed by thymidine incorporation. Growth and differentiation markers were assessed by quantitative RT real-time PCR and western blot.

Results: KLF6 expression was reduced in 33/39 (85%) of patients compared to normal livers, and 25/39 (64%) had levels decreased by more than 50%.

KLF6 expression levels in HepG2 cells were comparable to those present in patient-derived tumors. Expression levels of KLF6 RNA and protein were increased to resemble the levels present in normal liver by retroviral infection. Proliferation was reduced by 60% in KLF6-expressing cells ($p<0.05$, n=3), accompanied by reduced expression of cyclin D1 (50%, $p<0.0001$), c-jun (30%, $p<0.05$), beta-catenin (35%, $p<0.05$), TGFbeta1 (30%, $p<0.001$), and VEGF (50%, $p<0.005$), and significantly increased expression of E-cadherin (x3,5 fold, $p<0.005$), albumin (x1.7 fold, $p<0.05$) and TTR (x3 fold, $p<0.005$).

Conclusion: Wild type KLF6 levels are reduced in the large majority of HCC tumors, and almost 2/3 of tumors had decreases of more than 50% when compared to normal live. Reconstitution of KLF6 levels to a "normal" range in the HepG2 cell line resulted in marked growth suppression and increased differentiation. These findings support a role of KLF6 in growth suppression in normal hepatocytes, and suggest that its downregulation or loss in tumors may contribute to growth and de-differentiation characteristic of HCCs.

Acid Buffering Gels as Topical Microbicides to Prevent Transmission of Genital Herpes and Other STI. A.C. Garcia Tuyama. Mount Sinai School of Medicine, New York, NY.

Background: There is an urgent need to develop strategies to prevent HSV transmission. The acidic vaginal milieu (pH ~ 4.0-4.5) is presumed to inactivate STI, but is neutralized by semen (pH 7.2-8.0). The notion that acidic pH provides innate resistance led to the development of acid buffering products as microbicides. However, the extent and mechanism of anti-HSV activity is not known. These studies were designed to examine the anti-HSV activity of acidic pH, mechanism of activity, and to evaluate *Acidform,* which buffers to pH ~ 4.5, in a murine genital herpes model.

Methods: HSV-2 isolates were mixed with citrate buffer (pH 4.5 and 7.0), neutralized to pH 7.0, inoculated on human cells and plaques counted. Bioadhesive properties preclude testing *Acidform* in culture. Kinetic, binding, and nuclear transport studies were conducted and the impact on glycoproteins evaluated by SDS-PAGE. A murine genital herpes model assessed *Acidform* activity. Controls included placebo gel and PRO 2000, a microbicide in clinical trials that reduces HSV titer by > 4–5-logs *in vitro*. Mice were pretreated with the gels intravaginally, challenged 15 min later with a clinical isolate delivered in PBS or semen and monitored for infection.

Results: Exposure of HSV to pH 4.5 followed by neutralization reduced infection by >90%. Kinetic studies indicated that inactivation occurred within 30 min. Pretreatment of HSV-2 with pH 4.5 reduced binding and nuclear transport and modified gB mobility from dimeric to monomeric forms. 22/25 (88%) of mice who received placebo gel developed disease. In contrast, only 5/26 (19%) mice in the *Acidform* group and 0/10 in the PRO 2000 group developed disease. Aciform retained activity if mice were challenged with virus delivered in semen. The cytokine response to HSV, characterized by a rapid increase in IL-6 and IFN-γ was significantly reduced in mice treated with *Acidform. In vitro* studies indicate that PRO 2000 and acidic pH act synergistically to inhibit HSV infection.

Conclusions: These results suggest that acidic pH modifies the viral envelope to prevent binding and entry. *Aciform* offers considerable protection against HSV infection in the murine model and may be an optimal vehicle for formulation of acid-stable topical microbicides to prevent acquisition and transmission of HSV.

Mouse Embryoid Bodies (EBs) as Surrogate for Human Renal Embryonic Stem (ES) Cells: A Novel Source to Identify Candidate Markers for Renal Stem Cells. C. Vigneau, K. Polgar, D. Hyink, G. Striker, G. Keller, C. Burrow, and P. Wilson. Mount Sinai School of Medicine, New York, NY.

End-stage renal disease is a major cause of morbidity and mortality and its prevalence is increasing dramatically. The only therapies currently available are renal replacement by transplantation or dialysis. As the supply of donor kidneys is largely inadequate, more than one-half of the patients will remain on the waiting list permanently. Therefore, new therapies to preserve renal function or reverse renal damage are a high priority and utilization of stem cell is an exciting new option. In adult, both bone marrow and kidney niches have been found to contain stem cell. But the major question remains how to identify specifically renal stem cells (RSC) and how to obtain them in sufficient quantity.

Embronic stem cells (ES) cells are by definition "totipotent" and can generate any cell in any organ. ES can be cultured and maintained undifferentiated in presence of leukemia inhibitory factor (LIF). Without LIF, ES cells differentiate *in vitro*, and generate colonies known as EBs that contain developing cells of many lineages. The renal potential of the ES/EBs system has not been so far investigated. Our hypothesis is that mouse ES cells can give rise to tubular progenitors which are functional and can be integrated in the developing kidney *in vitro* and *in vivo*.

As there is no specific marker for potential RSC, we used a kidney specific combination: *brachyury*, WT-1, Cadherin-11, Pax-2 and Wnt-4. We first determined that after 4 days in culture in serum free conditions, in Activin 10 ng/mL, EBs give rise to cells which express *Brachyury*, WT-1, Cadherin-11, Pax-2 and Wnt-4. Since we used a cell line with GFP knocked in the still functional *brachyury* locus and with ß-gal gene expression, these cells can be FACS sorted for *Brachyury* and followed for ß-gal expression.

We next tested the functionality of the sorted cells in two different models: *in vitro* injection of cells into embryonic kidney in culture and *in vivo* injection of cells into newborn kidney. Embryonic kidney in culture is a well-defined model to follow development of every renal cells for a few days but not vascular cells. After injection of ß-gal RSC, cultured 4 days in Activin 10 ng/mL and FACS sorted for GFP, we found ß-gal cells GFP(+) in glomeruli and tubular cells and ß-gal cells GFP(-) in the ureteric bud.

Then we injected the same ß-gal FACS sorted GFP(+) cells into the left kidney of newborn mice (5 days old). This technique, recently developed in our laboratory, takes advantage of the neogenic zone in newborn mice, and allows the study of renal development *in vivo*. After 5 days after birth, only the tubular cells continue to develop in the mouse kidney. Two weeks after injection, we sacrificed the mice and stained the kidneys for ß-gal. Beta-gal cells have been found in almost all the proximal tubules of the outer cortex of all the left kidneys injected and never in the right kidney of the same animals.

Our data showed for the first time that EBs can give to RSC which can be integrated into the renal parenchyma. Next step will be to focus first on tubular stem cells, to identify more specifically, isolate, and enrich the tubular stem cell population. Same strategy will be also later use to purify podocytes or mesangial stem cells. This characterization will be key to the identification, isolation and expansion of tubular stem cells in adult repositories, such as the bone marrow or the kidney niche.

Alternative Splicing of the KLF6 Tumor Suppressor Gene During Early Stellate Cell Activation *in Vivo* Is a Proliferative Signal—Resolution of a Paradox. S. Yea, A. Katz, G. Narla, and S.L. Friedman. Division of Liver Diseases, Mount Sinai School of Medicine, New York, NY.

We previously cloned a novel zinc finger transcription factor, KLF6 (initially termed "Zf9"), which is induced as an immediate-early gene in hepatic stellate cells during liver injury *in vivo* (Ratziu et al., PNAS, 1998). KLF6 was then identified as an anti-proliferative tumor suppressor gene inactivated in several human cancers, and is also a key signal regulating adipogenesis through trans-repression of Dlk-1, an important inhibitor of this differentiation event. The finding that KLF6 is growth suppressive gene, yet rapidly induced when stellate cells undergo a proliferative burst, represented a paradox that has defied explanation. More recently, however, alternative splicing of KLF6 has been identified in rodents and humans, with generation of shorter, dominant negative isoforms that lack all or part of the DNA binding domain. These isoforms are increased relative to wt KLF6 in HCC, prostate and ovarian cancers, but their role in non-malignant tissue responses is not known. The aims of our study were: (1) to determine if early stellate cell activation leads to increased alternative splicing of KLF6; (2) to assess the biologic activity of KLF6 splice forms in cultured cells and (3) to define specific stimuli that regulate KLF6 alternative splicing.

Methods: We assessed KLF6 alternative splicing by PCR and Western blot in mouse stellate cells isolated at intervals following a single dose of CCl_4. The response of cultured stellate cells to key fibrogenic stimuli *in vivo* were assessed in a culture model.

Results: Alternative splicing of KLF6 increases during stellate cell activation *in vivo* and persists in activated stellate cells in culture. These splice proteins accumulate in the cytoplasm, have prolonged half-lives, abrogate wild type function as true dominant negatives that block induction/repression of wt KLF6 targets, and additionally lead to gain of function of transcriptional targets not ordinarily regulated by KLF6. KLF6 splicing is also induced in stellate cells by oxidant stress, and appear to be regulated by Ras activity. Using a splice-specific monoclonal antibody, these isoforms appear to be selectively expressed at a low level in stellate cells even in normal human liver.

Conclusions: Generation of alternative splice forms of KLF6 during stellate cell activation *in vivo* and in response to fibrogenic signals explains the paradox of its induction during the onset of a proliferative response of the cell type. Independent of its tumor suppressor activity, KLF6 appears to be an important signal regulating cellular differentiation, in part through the titration of full length vs. alternative splice forms. Alternative splicing of this transcription factor represents a novel mode of regulating gene expression not previously described in hepatic stellate cell biology.

Clinical Research

Tuberculous Dactylitis in a 46-Year-Old Male with HIV. S. Agarwal and D. Caplivski. Mount Sinai School of Medicine, New York, NY.

Extrapulmonary manifestations of tuberculosis have become increasingly important in the era of HIV/AIDS. We describe a case of tuberculosis (TB) dactylitis in a patient with AIDS who originated from the Ivory Coast. The diagnosis was established by direct visualization of acid fast bacilli on bone biopsy of the proximal phalanx. Tuberculosis should be considered in patients with unusual skeletal lesions, especially when an immunosuppressive condition is present. Ziehl-Neelsen staining and culture of tissue obtained via surgical biopsy offer the most direct approach to diagnosis.

Anger Justification and Blood Pressure: A Different Story for Men and Women over the Life-Span. N. Rieckmann[1], D. Abraham[1] and K.W. Davidson[2]. [1]Medicine, Mount Sinai School of Medicine, New York, NY, and [2]Medicine, Columbia University, New York, NY.

A constructive way of discussing one's anger (CABV) has been shown to be associated with lower resting systolic blood pressure (SBP). We hypothesized that overtly justifying one's anger (e.g., being determined to show one's own standpoint) would have an adverse effect on SBP.

BP medication-free men ($n=688$; age 18–90 years) and women ($n=604$; age 18–93 years) from a population-based, random sample underwent a stressful interview, which was rated for Anger Justification ($\alpha=0.88$). An average resting SBP score was computed from 4 readings ($\alpha=0.95$).

Surprisingly, Anger Justification was positively associated with CABV in both men ($r=.22$, $p<0.01$) and women ($r=.24$, $p<0.01$), and negatively associated with SBP for women only ($r=-.12$; $p<0.01$). Regression analyses were conducted; age, body mass index, parental history of MI, weekly alcohol intake, current smoking status, weekly physical activity, and education were entered first, and Anger Justificaton second. To examine age trends, the interaction term of age and Anger Justification was entered third. In men, Anger Justification was a significant predictor with only 1% of variance explained ($p<0.05$), but controlling for CABV rendered it insignificant. In women, no additional variance was explained by Anger Justification, but the interaction was significant ($p<0.05$), and remained significant when controlling for other psychosocial measures (CABV, anxiety, depression, hostility). Post-hoc analyses revealed that only in women over 65 years of age did Anger Justification significantly predict lower SBP (5% of variance), controlling for standard risk factors.

Thus, Anger Justification seems to have a strong beneficial effect for older women, but not for men at any age. Possible cohort, developmental, and methodological explanations for this benefit will be discussed.

Insulin Initiation in Poorly Controlled Diabetics. S.J. Adamcik. Mount Sinai School of Medicine, New York, NY.

Context: The decision to initiate insulin therapy in patients with type 2 diabetes is influenced by many factors including measured indices of glycemic control, presence of diabetes related comorbidities, and provider/patient preferences.

Objective: To determine if the presence of a specific macrovascular event or outcome in a poorly controlled diabetic patient correlates with an Internal Medicine resident's decision to initiate insulin therapy.

Design, Setting, Population: The Internal Medicine Associates (IMA) is the continuity clinic for the Mount Sinai Internal Medicine residency training program and serves a population of patients with a high prevalence of type 2 diabetes—the East Harlem section of New York City. The medical record of 500 IMA patients with type 2 diabetes will be reviewed and information regarding level of glycemic control, presence of macrovascular disease and pharmacologic diabetic regimen will be recorded and analyzed.

Main Outcome Measure: Rates of insulin initiation in type 2 diabetic patients with documented evidence of macrovascular disease.

Hypothesis: In Type II diabetic patients with laboratory evidence of poor glycemic control (HgbA1c levels >7.5), Internal Medicine residents at a large inner city clinic are more likely to initiate insulin therapy in those patients with documented evidence of macrovascular disease as compared to those with no evidence of macrovascular disease.

Conclusions: (Preliminary-ongoing data analysis). Poorly controlled patients with documented evidence of macrovascular disease had a statistically significant greater incidence of insulin use.

Utility of CACS in Assessing Cardiovascular Risk in a Lipid Specialist's Practice. A. Aronovitz. Mount Sinai School of Medicine, New York, NY.

Coronary calcium scores have been proposed as a method to predict cardiac risk. It has been shown that the calcium score on electron beam computerized tomography (EBCT) correlate with plaque burden. As a result, it has been suggested that EBCT may be used as a screening tool to identify patients with arteriosclerosis, and therefore, at greater risk for CHD. Initial studies have supported this theory, and in fact, the ATP-III guidelines recommend EBCT for patients at intermediate cardiac risk. We would like to perform a retrospective analysis on 170 patients at low to intermediate cardiac risk who have had EBCT between 1998–2004. The study will assess whether coronary calcium scores provide added value to the Framingham risk score (FRS) alone when evaluating cardiac risk.

Cerebrospinal Fluid Pleocytosis in HAART-Era AIDS Cohort: Clinical Correlations. A. Borad, L. Estanislao, S. Wallenstein, S. Hossain, and S. Morgello. Mount Sinai School of Medicine, New York, NY.

Background/Objectives: Cerebrospinal fluid (CSF) pleocytosis is known to occur in individuals with HIV infection. We determine the presence of CSF pleocytosis, and its relation to antiretroviral usage, as well as its impact on the neuropsychologic performance and neurologic status of subjects enrolled in Manhattan HIV Brain Bank, a prospective study of an advanced AIDS cohort.

Methods: Data from subjects who underwent serial lumbar puncture (LPs), clinical, neuropsychologic (NPE) and neurologic examination (NE) every 6 months from January 1999 to October 2004 were obtained.

Results: There were 107 subjects (30 females, 77 males) of whom 32 (30%) had at least one episode of cerebrospinal fluid (CSF) lymphocytic pleocytosis (WBC ≥ 6 c/uL). Subjects with opportunistic brain infections were excluded. There were a total of 365 LPs performed. The presence of CSF pleocytosis correlated with the absence of antiretroviral (ARV) use at the time of the LP (21 CSF pleocytosis off ARV vs. 251 without CSF pleocytosis on ARV) (Fisher's exact test 0.001).

Conclusion: HIV-infected individuals on antiretrovirals are less likely to have CSF pleocytosis.

Geriatric Ambulatory Medical Education for Internal Medicine (IM) Residents: The Need for Faculty Development. C. Chang, E. Widera, L. Fry, S. Bradley, D. Thomas, E. Chai, and R.M. Leipzig. Supported by: Departments of Geriatrics and Internal Medicine, Mount Sinai School of Medicine, New York, NY.

Background: National surveys indicate a need for additional training in geriatrics during IM residencies. Though MSSM IM residents receive an excellent introduction to inpatient geriatrics during their ACE Unit and Geriatric Consult Service rotations, no formal ambulatory geriatric curriculum exists.

Objective: To identify IM resident and precepting faculty needs for formal education in geriatric ambulatory care.

Method: A Needs Assessment Survey was developed and administered to all IM residents and precepting faculty in June 2004. Baseline personal and education demographics were obtained. Respondents were asked to rate 19 geriatric ambulatory care topics using a 5-point Likert-type scale in terms of: (1) importance for internists to learn during residency, (2) actual training during ambulatory block, continuity clinic and house calls, (3) adequacy of training and (4) perceived capacity of IM faculty to teach geriatric ambulatory topics.

Results: A total of 50 residents (45.4%) and 27 faculty (65.9%) completed the survey. Both faculty and residents felt that all 19 geriatric ambulatory topics were important (range of means 3.766-4.633, where 0=least and 5=most important). However, only certain topics were actually and adequately taught. These topics were mostly disease states common in the elderly (e.g., CAD and DM) rather than geriatric syndromes or functional assessment. Both faculty and house staff felt that these topics were important and that the faculty were capable of teaching them. Because faculty felt less comfortable teaching geriatric syndromes and functional assessments, these topics were taught less frequently or adequately, and were generally ranked as less important for internists to learn.

Conclusion: Though IM residents and faculty ranked the 19 geriatric ambulatory topics as need-to-know, only topics that faculty felt they had good capacity to teach were actually and adequately taught and felt, by both groups, as important for internists to learn—the result is that residents do not believe it is important to learn topics which the faculty do not feel competent to teach. For house staff to graduate competent in caring for ambulatory geriatric patients, precepting IM faculty will need to learn the content and how to teach these other important geriatric ambulatory care topics.

Searching for Cardiac Sarcoidosis. A.S. Teirstein[1], Z.B. Frankel[2], A.J. Einstein[2], D. Mehta[2], M.L. Padilla[1], and M.Iannuzzi[1]. [1]Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, and [2]Department of Cardiology, Mount Sinai School of Medicine, New York, NY.

The following abstract has been submitted to the WASOG conference.

In the United States, clinical cardiac sarcoidosis is reported in approximately 5% of patients, and at autopsy in 25%. Ventricular arrhythmias and myocardial failure are the common presenting clinical manifestations. Unfortunately, in many patients cardiac disease is occult and sudden death is the initial presentation. All patients with sarcoidosis are at risk for cardiac involvement. A variety of cardiac studies have been employed in the diagnosis. The requisite minimal tests to screen patients and the studies required to follow patients have not been clearly delineated. Indications for implantation of electrical devices are not entirely clear. Recently, PET scans and MRI scans have exhibited value in the diagnosis and follow-up of cardiac sarcoidosis. At the Mount Sinai Medical Center, NY, 100 patients with biopsy proven sarcoidosis have been enrolled in a study in an attempt to generate an algorithm for the proper diagnosis and treatment of cardiac sarcoidosis, and the indications for implantation of cardioverter defibrillators. All 100 were screened with complete history, physical examination, standard chest radiography, pulmonary function studies, blood tests, EKG, Holter monitor and echocardiograms. Twenty-six patients with abnormal cardiologic screen were referred for PET scan and MRI scans. Demonstration of cardiac arrhythmias prompted placement of cardioverter devices. MRI and PET scans demonstrated sarcoidal cardiac abnormalities, often affecting medical therapy.

The Incidence of Protease Inhibitor-Associated Mutations in Patients Taking Atazanavir. D. Caplivski[1], C. Salama[1], and D. Caplivski[2]. [1]Mount Sinai School of Medicine, Elmhurst Hospital Center, Elmhurst, NY and [2]Mount Sinai School of Medicine, New York, NY.

Background: Atazanavir is a new protease inhibitor (PI) used in HIV treatment. The signature protease gene mutation associated with atazanavir resistance is I50L. There is limited data about other mutations associated with the clinical use of atazanavir.

Methods: The Elmhurst Clinic Database consists of 1240 genotype tests (GT) from 743 patients at the Elmhurst Hospital Immunology Clinic. Forty-three patients had undergone GT while taking atazanavir and were divided into 3 groups: 1. Patients with no prior PI experience (n=10). Six used concomitant ritonavir, 4 did not. 2. Patients with PI experience, but without significant PI-associated mutations (n=15). Eleven used concomitant ritonavir, 4 did not. 3. Patients with previous PI therapy and significant PI mutations (n=15). Fourteen used concomitant ritonavir, 1 did not.

Results: Group 1: No significant new PI mutations were detected. New polymorphisms detected included L63P, V77I. Mean viral load at GT was log 4.5. Group 2: One patient who had previously taken nelfinavir manifested a D30N on GT. No other significant mutations were detected. New polymorphisms detected included M36I, K45R, G73S, L63P, I93L. Mean viral load at time of GT was log 4.9. Group 3: Significant pre-existent mutations seen in this group included 1 with D30N, 9 with M46I, 3 with G48V, 1 with I50V, 7 with I54V/T, 8 with V82A/F, and 11 with L90M. After atazanavir use one patient manifested a V82A/S and an L90M. This patient was taking atazanavir with agenerase and norvir, but no nucleoside backbone. No other significant mutations developed and no patients developed the I50L or N88S mutations. New polymorphisms detected included K20I/R, F53L, G73S, T74A/S, I93L. Mean viral load at time of GT was log 4.5. The mean duration of therapy prior to GT was 5.13 months.

Conclusions and Summary: Patients taking atazanavir are at low risk for significant new PI-associated mutations early during virologic failure.

Genes and Pathways Involved in the Molecular Pathogenesis of Hepatocellular Carcinoma in HCV-Cirrhotic Patients. Y-B Chen, E. Wurmbach, S. Roayaie, I. Fiel, M. Schwartz, S. Thung, G. Khitrov, W. Zhang, V. Mazzaferro, J. Bruix, E. Bottinger, S. Waxman, S. Friedman, and J.M. Llovet. Mount Sinai Medical Center, New York, NY, and Istituto Nazionale di Tumori, Milan, Italy, Hospital Clinic, Barcelona, Spain.

The molecular pathogenesis of hepatocellular carcinoma (HCC) is complex, and insufficient data are available on the key genes involved in the initiation and progression of liver carcinogenesis. To characterize the gene expression profiles of pre-neoplastic lesions and HCC in cirrhotic patients due to hepatitis C virus (HCV) infection, we assessed the expression patterns of 52 genes that have previously been associated with liver carcinogenesis in 78 samples from 52 patients by quantitative Real-Time RT-PCR. The samples represented all stages of the stepwise progression process with emphasis on the transition from preneoplastic lesions to HCC: normal tissue (10), cirrhotic tissue (10), low grade dysplastic nodules (10), high grade dysplastic nodules (8) and four stages of cancer from very early HCC to metastatic tumors/gross vascular invasion (40). Specific mRNAs were quantified by using probe/primer sets from *Taqman Gene Expression Assays* and altered key genes were further confirmed using additional primers by SYBR Green method.

We identified genes that were significantly up-regulated across the spectrum of the hepatic carcinogenetic process such as TERT, STK6, Glypican-3, survivin and TOP2A, as well as others that were down-regulated such as XLKD1, E-cadherin, IGFBP3, and HGF [ANOVA, p=0.001 for all]. Some other gene alterations observed were more stage-specific. Dysplastic nodules already harbored significant de-regulated genes compared with cirrhotic or normal liver tissue. Logistic regression analysis identified LYVE1 (8-fold down regulation in HCC, p=0.0001), E-cadherin (2.5-fold down-regulation in HCC, p=0.001) and survivin (2.3-fold up-regulation in HCC, p=0.001) as the most informative genes to discriminate dysplasia from early cancer. In addition, we found a 3-gene model that correlated with the metastases of HCC. Our results indicate an common activation of Wnt signaling pathway in early HCC, and potential involvement of EGF receptor tyrosine kinase activated pathways in a sub-population of HCCs: EGF showed a 5-fold up-regulation in 17/40 HCCs (vs. 0/28 cirrhosis and pre-neoplastic nodules, p=0.0001), and SOCS1 was significantly down-regulated in 10/40 HCCs in comparison with 0/10 cirrhotic tissue (p=0.01).

These data provide a comprehensive profile of key changes in gene expression and signaling pathways associated with the stepwise progression of HCC due to HCV infection. Further studies with DNA microarrays and biochemical methods are underway to complement this approach.

Predictors of Death among a Homebound Admission Cohort of a Home-Based Primary Care Program. L DeCherrie[1], J Penrod[1,3], K Ornstein[2], T Hochman[3], and J Boal[2]. Departments of [1]Geriatrics and [2]Medicine, Mount Sinai School of Medicine, New York, NY, and [3]GRECC, Bronx VA Medical Center, Bronx, NY.

The number of frail, homebound people unable to get to the doctor is increasing. Homebound patients, who tend to have multiple medical problems and poor functioning, often are unable to get primary care. Programs where physicians make home visits are increasing. It is likely that home-based primary care patients represent a vulnerable cohort, but little is known about their overall prognosis.

Objective: To examine risk factors for death in homebound patients in a home-based primary care program (HBPCP).

Methods: Retrospective chart review of new enrollees in a HBPCP (n=262) between 1/03 and 6/04, followed until death (n=35), discharge (n=26), or study termination (11/04). A Cox proportional hazards model was used to examine the relationships among demographic and clinical characteristics at admission and mortality.

Results: The sample included 193 (80%) women, 86% ≥65 years (25 – 102 yrs), 24% black, 23% Latino and 50% white, 59% had dementia, 6% had pressure ulcers, mean Charlson co-morbidity score 2.25, and 66% were dependent in ≥ 4ADL's. The mortality rate was 10.4% and 16.3% at 6 and 12 months after admission. An increased risk of mortality was associated with being older (HR, 1.05, 95%CI, 1.01 – 1.10), having a high school degree (HR, 3.69, 95%CI, 1.03 – 13.25), living with family compared to a paid caregiver (HR, 3.23, 95%CI, 1.15 – 9.09), having more comorbidities (HR, 1.46, 95%CI, 1.16 – 1.85), pressure ulcers (HR, 7.56, 95%CI, 1.86 – 30.71), and ≥6 prescription medications (HR, 11.01, 95%CI, 2.38 – 51.03), being dependent in all ADL's (HR, 14.22, 95%CI, 1.56 – 129.68), and having a home attendant ≥85 hours per week (HR, 3.87, 95%CI, 0.96 – 15.58). The risk of mortality was lower for patients with dementia (HR, 0.25, 95%CI, 0.10–0.65) and independent in 2 – 3 IADL's (HR, 0.16, 95%CI, 0.23 – 2.09). Gender, ethnicity, Medicaid, depression, incontinence, peg tube, falls, recent hospitalization, and caregiver stress were unrelated to mortality risk.

Conclusions: Homebound people, even those connected to a HBPCP, have a high risk of mortality, similar to the rate found in a community based long-term care program. Mortality was higher for patients with more functional impairments and multiple illnesses, including pressure ulcers at enrollment. These findings highlight the vulnerability of this cohort and should be considered by clinicians who will care for this growing population.

Effect of Novel Combination Therapies in the Treatment of Chronic Hepatitis B. A. Ala, N. Karanth, T. Foster, and D. Dieterich. Division of Liver Diseases, Mount Sinai School of Medicine, New York, NY.

Introduction: Interferon, adefovir, and 3TC (lamivudine), are approved for the treatment of hepatitis B (HBV), FTC (emtricitabine) and tenofovir (TDF) are approved for HIV but exhibit significant HBV activity. Hitherto, there has been little data on the use of combining these agents in the treatment of chronic hepatitis B. Utilizing two (or more) nucleoside analogues, as used in the treatment of HIV, is theoretically sound. It should maximise viral suppression, thereby reducing the chance that resistance will develop. We used some of these drugs in combination to treat naïve HIV seronegative patients with chronic HBV.

Aims: In this pilot study we report our overall experience with combination therapy in mono-infected patients. Our study was to assess the effect of combined drug regimens on viral load and seroconversion in the treatment of patients with chronic HBV.

Methods: Fifteen patients (age 30–54, 11 males and 4 females) with chronic HBV were followed from 6 months-9 years. They were divided into the following treatment regimens: Group 1 (n=4): 3TC and/or 3TC+famciclovir followed by addition of TDF or increasing doses of 3TC to 300mg. Group 2 (n= 6): Adefovir followed by supplementation of 3TC (300mg) or TDF. Group 3 (n=5): any other monotherapies (e.g., Interferon, Entecovir, FTC) followed by combination therapy (including 3TC 300mg and/or TDF).

Results: Six of the 7 patients who were given increased doses of 3TC (300mg) were able to maintain sustained viral suppression; prior treatments on monotherapy had yielded at best only refractory improvements in viral suppression until that point. Of these, two were found to have seroconverted after 4 and 20 weeks respectively. Three precore mutants were part of this sub-cohort, one of whom was the only failure of therapy in this study. All patients (total of six, including 2 precore mutants) who were treated with TDF as salvage therapy showed sustained viral suppression. There was no evidence of seroconversion in this subset of patients. Two patients originally included in the study were lost to follow up.

Conclusion: Combination therapies may be an effective treatment in those patients with chronic HBV who fail to respond to conventional management. Our experience shows TDF as a viable salvage therapy for suboptimal response to adefovir. Furthermore, the addition of 3TC at increased doses (300mg vs. 150mg) proved to be effective in the suppression of HBV DNA levels, from 12 weeks up to greater than 2 years after implementation of therapy. Precore mutants benefit from 3TC supplementation to adefovir. Clearly a larger cohort of patients is required to assess combination future chronic hepatitis B therapy.

Statin Therapy and Acute Coronary Syndrome: The Common Practice at Mount Sinai. T. Pilar and P. Stevens-Cohen. Mount Sinai School of Medicine, New York, NY.

Recent data has emerged in the field of cardiology suggesting that maximum dose lipid lowering agents have decreased mortality and morbidity in patients with acute coronary syndrome (ACS). Many of the studies used maximum therapy regardless of baseline lipid profiles. This data has changed the way we manage ACS at Mount Sinai. Traditionally, such patients were started on lipid lowering agents on a dose that was largely determined by their lipid profile. These patients would be followed by their primary care physicians and cardiologists, who would titrate lipid-lowering agents to a goal LDL <100. Currently, patients with ACS are being discharged on maximum therapy regardless of their lipid profile making us redefine the role of lipid profiling in ACS. (There is also data stating that lipid levels are not accurate in the setting of ACS due to its highly inflammatory state).

While there is data supporting this treatment, there is no current standard of care regarding the duration of therapy. Furthermore, if patients are being started on intense cholesterol lowering medicine regardless of initial lipid profile, how are these medicines adjusted on an out-patient basis? Has the old standard of LDL <100 changed? The side effect profile of cholesterol agents is well defined. Since we are starting to use higher dose therapy, we expect to see a higher incidence of myositis and liver function abnormalities.

We conducted a survey of medicine housestaff, attendings, cardiology fellows and attendings to see if there is a standard of care at Mount Sinai. We proposed that housestaff and cardiologists rotating through the CCU, would be more likely to discharge patients home on high dose statin therapy, regardless of initial lipid profile. There is no standard of time regarding the length of treatment. The purpose of the second half of the questionnaire was to survey how long patients were being treated with statins and how the medications were being titrated.

Impact of Ambulatory BP Monitoring on Living Kidney Donation. E. Herman. Mount Sinai School of Medicine, New York, NY.

Background: Living kidney donation is becoming increasingly important in kidney transplantation, due to improved graft and patient survival in recipients from living donors versus cadaveric donors, as well as avoidance of a lengthy waiting list and the possibility of pre-emptive transplant. Most transplant centers exclude hypertensives from kidney donation due to concerns of worsened renal and BP outcomes. Ambulatory BP monitoring (ABPM) measures BP multiple times over a 24-hour day in a patient's usual setting. ABP is more closely associated with evidence of target-organ damage and is a better predictor of cardiovascular events than clinic BP (CBP). ABP allows identification of white-coat hypertension (WCH), those with elevated CBP but normal ABP; these patients have been shown to have risks of cardiovascular events similar to patients with sustained normotension. ABP also identifies "masked hypertension" (MH), when CBP is normal but ABP is elevated; these patients have target-organ damage and rates of cardiovascular events similar to sustained hypertensives.

Methods: Potential living kidney donors undergoing initial nephrology evaluation at the Recanati/Miller Transplantation Institute were invited to participate. Subjects wore a Spacelabs 90217 ABPM for 24 hours, during which time the monitor obtained BP readings every 20–30 minutes. Subjects with fewer than 10 daytime and 4 nighttime readings were excluded from the study. CBP was compared to mean 24-hour ABP for each subject. Hypertension by CBP was defined as ≥ 140/90, and hypertension by ABP was defined as ≥ 135/85.

Results: A total of 70 potential donors enrolled in the study. Demographic information is listed in Table 1.

Categorization as normotensive or hypertensive by CBP and ABP is shown in Table 2. 23 subjects were hypertensive by CBP. Of these, 18 (78%) were normotensive by ABP, giving a total prevalence of WCH of 26%. These subjects were medically cleared for donation. 2 subjects who were normotensive by CBP were found to be hypertensive by ABP, giving a prevalence of MH of 3%. These subjects were excluded from donation.

Table 1

	Male/Female	White	Black	Hispanic	Other race/ ethnicity
N	27/43	20	20	24	6
%	39/61	29	29	34	9

Table 2

		Ambulatory BP		
		Normotensive	Hypertensive	
Clinic	Normotensive	45	2	47
BP	Hypertensive	18	5	23
		63	7	70

Conclusion: There is a high-incidence of WCH in potential living kidney donors. The use of ABPM in initial evaluation of potential donors may expand the potential donor pool, while ensuring protection of potential donors by identifying those with MH.

Verification of the Efficacy of an Assay for Establishing Microbicide Use in a Pilot Clinical Study. A. Kasowitz[1], K. Hogarty[1], C. Goldberg[2], S. Patel[1], B. Herold[2], and M. Keller[1]. Divisions of [1]Medicine-ID and [2]Pediatric-ID. Mount Sinai School of Medicine, New York, NY.

Objectives: To evaluate an accurate, rapid, and inexpensive method for verifying participant use of single-use intravaginal plastic applicators in a pilot clinical microbicide study.

Study Design: In a published study, a trypan blue assay was developed to establish whether Microlax-type microbicide applicators had been exposed to the vagina. To verify this assay, single-use intravaginal plastic applicators were collected after use from 16 sexually abstinent, healthy women enrolled in a once-daily, placebo-controlled 14-day microbicide trial designed to evaluate safety. Participants inserted the first dose of 0.5% PRO 2000/5 Gel or Placebo Gel under the observation of the study clinician and were instructed to insert one dose each night at the hour of sleep for 13 subsequent days. Subjects were given a study diary to record time and date of gel use. Used applicators were placed into individual plastic bags and returned to the study staff at subsequent study visits. Each applicator was dyed with 0.4% trypan blue, air-dried for 5 minutes and rinsed gently in distilled H_2O. The first applicator used served as the positive control, and several unused applicators were dyed in the same fashion to serve as negative controls. Two blinded observers rated the applicators as used or unused and these results were compared to the subjects' self-reports.

Results: In 99% of cases, observers' findings correlated with the participants' self-reports; used applicators were easily distinguished from unused applicators. In a subset of cases, the examiners were able to distinguish between applicators that had been used intravaginally and applicators that had been filled with study gel and emptied *ex vivo*.

Conclusion: Trypan blue staining of single-use intravaginal plastic applicators is accurate, rapid, inexpensive, and correlated well with participant self-report in this study. This simple method could prove useful in interpreting data from future large-scale microbicide efficacy studies.

Dosing of Radiocontrast for Interventional AV Fistula Salvage Procedures in Stage 4 Chronic Kidney Disease Patients. K. Kian[1], C.M. Wyatt[1], D. Schon[2], J. Packer[2], J.A Vassalotti[1], and R. Mishler[2]. [1]Department of Nephrology, Mount Sinai Medical Center, New York, NY, and [2]Arizona Kidney Disease and Hypertension Ambulatory Surgery Center, Phoenix, AZ.

Background: The Dialysis Outcomes Quality Initiative emphasizes on increasing arteriovenous fistula prevalence, by promoting referral for fistula creation in patients with stage 4 chronic kidney disease (CKD). The aim of early fistula creation is to provide an optimal access for initiation of dialysis, thus avoiding central venous catheter use. The endovascular management of non-maturing fistulas is more complicated in these patients, where the expected benefit of catheter avoidance must be weighed against the risk of contrast induced nephropathy (CIN). This study describes the experience of an interventional nephrology center in performing endovascular procedures in patients with stage 4 CKD.

Methods: All consecutive endovascular procedures performed over a two-year period in patients with stage 4 CKD and non-maturing access were identified. Data collected included the type of procedure performed, amount of contrast used per procedure, pre, 2-day and 7-day creatinine, need for acute dialysis and the type of access used to initiate dialysis.

Results: A total of 65 procedures were performed in 34 patients. A mean dose of 7.8 mL of contrast was used per procedure. The incidence of CIN (25% increase in serum creatinine) was 4% at two days and 4.6% at one week. All values returned to baseline within two weeks, and no patient required acute dialysis. Among the 33 patients with fistulas, 15 had started dialysis using the fistula (45%), 13 (39%) remained in CKD, and 5 (15%) patients required a catheter at the initiation of dialysis.

Conclusion: This study demonstrates that in patients with advanced CKD, fistulas can successfully be salvaged with a low CIN incidence using very small contrast volumes.

Achieving Optimal Treatment Goals in Patients with Stage III Chronic Kidney Disease. V. Konduri[1], C. Wyatt[1,2], J. Eng[1], and R. Rohatgi[1,2]. [1]Department of Medicine, Bronx Veterans Affairs Medical Center, Bronx, NY, and [2]Division of Nephrology, Department of Medicine, Mount School of Medicine, New York, NY.

Background: Chronic kidney disease (CKD) is defined by the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines as a glomerular filtration rate (GFR) < 60 $mL/min/1.73m^2$ or the presence of microscopic/macroscopic albuminuria. Although CKD is estimated to affect more than 10% of adults in the United States, it often goes unrecognized because serum creatinine is an unreliable marker of GFR. The K/DOQI guidelines advocate the use of the Modification of Diet in Renal Disease estimation of GFR (MDRD eGFR) to identify and stage patients with CKD; however, the effect of routine GFR estimation on clinical practice has not been evaluated.

Hypothesis: We hypothesize that routine reporting of MDRD eGFR will increase ACE inhibitor utilization, blood pressure control, and measurement of urine protein.

Methods: We plan to compare clinical practice patterns before and after institution of routine MDRD eGFR reporting in the Bronx VA primary care population. To minimize the effects of evolving practice guidelines, we will compare the periods immediately before and after implementation of eGFR reporting. The data presented in this abstract reflect the pre-eGFR reported group where the baseline practice patterns were measured. All individuals with a measured serum creatinine between July 1, 2003 and June 30, 2004 were included in this study. Of these patients the following data was extracted from the chart: age, race, gender, ace inhibitor (ACEi) or angiotensin receptor blocker (ARB) use, urinalysis, last recorded blood pressure and history of diabetes. The abbreviated MDRD calculation was used to determine eGFR.

Results: 15,155 patients of the 21,285 Bronx VA patients had a measured serum creatinine and, of these individuals, 2,564 (16.9%) patients had an eGFR ≤ 59 $mL/min/1.73m^2$. 14.5 % (2,201/15,155) of patients had stage III CKD (30–59 $mL/min/1.73m^2$) with an average age of 75.0±9.8 years old and serum creatinine of 1.58±0.29 mg/dL. Approximately 30% (661/2201) of stage III CKD patients were diabetics. Since ACEi/ARBs are known to decrease the progression of diabetic nephropathy and this population had a high prevalence of diabetes, we stratified stage III CKD patients into diabetics and non-diabetics under the hypothesis that diabetes is a much more potent marker for ACEi/ARB utilization than CKD itself. We then evaluated care in both groups by studying ACEi/ARB utilization, achievement of blood pressure control (<130/80) and urinalysis testing. Only 47.7 % (735/1540) of non-diabetics vs 85.3% (564/661) of diabetics were prescribed ACEi/ARBs. Similarly, urinalyses were underutilized in non diabetics (47.8%; 736/1540) vs. diabetics (74.6%; 493/661) with CKD. However, blood pressure control of <130/80 was achieved in 48.1% (741/1540) of non-diabetics vs. 35.2% (233/661) of diabetics with CKD.

Conclusions: ACEi/ ARB and urinalysis utilization amongst diabetic patients is greater than in non-diabetics with stage III CKD; however, achievement of optimal blood pressure control in non-diabetic patients is more common than in diabetic patients with CKD.

Speculation: We speculate that the routine laboratory calculation and reporting of estimated GFR will increase the awareness of CKD and increase utilization of treatments, like ACEi/ARBs, in non-diabetics patients with renal disease which will reduce the number of patients developing end-stage renal failure.

Cervical Cancer Screening among Women with Hysterectomies by Provider Type. B.G. Lewis, E.A. Halm, and A.D. Federman. Mount Sinai School of Medicine, New York, NY. (Tracking ID # 134166).

Background: Since 1996, the U.S. Preventative Task Force has recommended against cervical cancer screening in women without a cervix. Yet, as recently as 2002, 69% of such women reported getting a pap smear within the previous 3 years and the factors influencing this pattern of care remain vague. Because both gynecologists and generalists perform pap smears, we examined the association between provider type and pap smear rates among post-hysterectomy women.

Methods: We analyzed data from the 2000 National Health Interview Survey (NHIS), a cross-sectional, nationally representative annual survey of self-reported health and health care utilization among adults (n = 32,374). We included post-hysterectomy women ages 18–65. We excluded those with a history of abnormal pap smears, breast, cervical, endometrial or ovarian cancer, current pregnancy and recipients of Medicare. We determined pap smear rates in the past 12 months, stratified by provider type: generalist (gen); gynecologist (gyn) or both. We used multiple logistic regression to assess the relationship between pap smears and provider type, adjusting for age, race, education, income, insurance status, census region, smoking and health status. SUDAAN statistical software was used to account for the NHIS sampling design.

Results: The analysis included 1,221 women, representing 7.3 million women nationwide. 53% received care from a gyn, 26% from gen, and 20% from both. The mean ages of the women were 49 years in gyn, 53 in gen, and 51 in both. Women in the 3 provider groups differed significantly by black race (41%, 33%, 25%; $p=0.001$), married (77%, 67%, 72%; $p=0.039$), uninsured (57%, 32%, 11%; $p=0.042$), urban residence (46%, 29%, 24%; $p<0.001$), and having 1 chronic illness (54%, 26%, 19%; $p=0.003$). They did not differ significantly by income, immigration status, Census region, or smoking status. Overall, 55% had a pap smear in the previous 12 months. 85% of women in the gyn group underwent Pap smears; 44% in gen, and 73% in both gen/gyn ($p<0.001$). In multivariate analysis, women who visited gyn were more likely than those cared for by gen alone to have had a pap smear (Adjusted OR 4.44, 95% CI 2.21 – 8.91). The effect was less pronounced when women visited both (AOR vs. gen: 1.47, 95% CI 0.62 – 3.50).

Conclusions: Approximately 4 million pap smears are performed each year on women who have had hysterectomies though cervices are only left in <5% of cases. Gynecologists perform the majority of these pap smears; however, a large number of such women receiving care from generalists continue to undergo this service. Additional research is needed to identify the physician and patient factors that influence the use of pap smears in post-hysterectomy patients and to prevent unnecessary care.

Comprehensiveness of Preventative Care among Women Seen by Generalists, Gynecologists or Both B.G. Lewis, E.A. Halm, and A.D. Federman. Mount Sinai School of Medicine, New York, NY.

Background: Both gynecologists and generalists provide preventative care to women. However, the effect of provider type on the delivery of preventive care remains unclear. We examined use of preventive services as recommended by the US Preventative Task Force, among women seen by generalists only (gen), gynecologists only (gyn) or both.

Methods: Using cross-sectional data from the 2000 National Health Interview Survey (NHIS), we studied self-reported receipt of preventative services for women ages 18 – 65 (n=10,347). We excluded women with a history of breast, colorectal, cervical, endometrial or ovarian cancer, current pregnancy and recipients of Medicare. For women ages 18 – 65, we analyzed the association of provider type with rates of pap smears (excluding those with a history of hysterectomy), tobacco use screening and exercise/diet counseling; for women 50 – 65, biannual clinical breast exams (CBE), mammograms, and colon cancer screening were also analyzed. We modeled each outcome using multivariate logistic regression, and total number of services using Poisson regression, and controlled for age, education, income, race, insurance type, comorbidities. The analysis was weighted to account for the multilevel sampling design of the NHIS.

Results: Women seen by gen (15%), gyn (62%) and both (23%) differed by age (43 yrs, 37, 39, respectively, $p<0.01$), black race (18%, 48%, 33%, $p<0.01$), college-education (12%, 61%, 26%, $p<0.01$), and having ≥ 1 chronic disease (16%, 60%, 22%, $p<0.01$). The mean number of services by provider type were, for women <50, 1.9 (gyn), 1.5 (gen) and 1.9 (both) ($p<0.01$), and for women 50 – 65, 4.3 for gyn, 4.0 for gen, 4.2 for both ($p<0.01$). These findings remained significant in adjusted Poisson regressions for women <50 (β: gyn, 0.22, $p<0.01$; both, 0.24, $p<0.01$) and 50 – 65 (β: gyn, 0.09, $p<0.01$; both, 0.11, $p<0.01$). Women 18 – 65 seen by gyn or both were more likely to have pap smears (gyn vs. gen, adjusted OR 11.06, 95% CI 6.87 – 17.80; both vs. gen: 11.47, 6.25 – 21.07) and tobacco use screening (gyn vs. gen: 1.15, 0.93 – 1.42; both vs. gen: 1.28, 1.00 – 1.64). Gyn patients tended to receive diet/exercise counseling less than gen (diet: 0.88, 0.69 – 1.12; exercise: 0.91, 0.73 – 1.14). Among women 50 – 65, gyn and both gyn/gen patients were more likely than gen patients to have mammograms (gyn vs. gen: 2.95, 1.48 – 5.87; both vs. gen: 3.59, 1.48 – 8.70) and CBE (gyn vs. gen: 3.31, 1.81 – 6.04; both vs. gen: 4.38, 2.13 – 9.03). There was no significant difference in colon cancer screening. Among women 18 – 65 with no chronic health problems (n=1528), receipt of preventive care did not differ significantly except gyn and both continued to perform significantly more mammograms (AOR, 95% CI: gyn: 3.59, 1.52 – 8.48; both 5.06, 1.72 – 14.89) and pap smears (gyn: 10.57, 6.00 – 18.62; both: 10.77, 5.46 – 21.24) than gen.

Conclusions: Women seen by gyn alone or both gyn and generalists receive more preventative services compared to those seen by generalists alone. Collaborative gyn/generalist care may not be necessary to ensure comprehensive preventive care for many women. Moreover, these findings further validate the role of gynecologists as primary care providers for many women.

Statins, Angiotensin Receptor Blockers, and Steroid Weaning Are Associated with Reduced Mortality among Heart Transplant Recipients. S.A Lubitz, D.A. Baran, M.J. Zucker, L.H. Arroyo, M. Chan, M.C. Courtney, R. Correa, D. Spielvogel, S.L. Lansman, and A.L. Gass. Mount Sinai School of Medicine, New York, NY.

Background: Immunosuppressive strategies and post-transplant pharmacologic regimens continue to evolve for cardiac transplantation. The current study examined the associations of common post-transplant immunosuppressive and adjunctive medications with the long-term survival of cardiac transplant recipients.

Methods: We reviewed demographic, clinical, and pharmacologic data from 220 consecutive patients that received heart transplants between 1986 and 2003 and survived beyond 3 months. Immunosuppressive regimens were cyclosporine (n=94) or tacrolimus (n=126) based, and 104 patients were successfully weaned off steroids (all receiving tacrolimus). Significant univariate predictors of mortality ($p<0.20$) were subsequently analyzed in a Cox proportional hazards analysis.

Results: The mean follow-up was 52 ± 13 years. Overall survival was 96%, 88%, and 81% at 1, 3 and 5 years, respectively. Significant multivariates associated with mortality included pretransplant diabetes mellitus (hazard ratio [HR] 2.83, 95% confidence interval [CI] 1.45 – 5.04), black race (HR 1.41, 95% CI 1.01 – 1.94), higher pre-transplant creatinine clearance (HR 0.99, 95% CI 0.98 – 1.00), removal from steroids (HR 0.60, 95% CI 0.39–0.85), and exposure to a statin (HR 0.53, 95% CI 0.40–0.70) or ARB (HR 0.50, 95% CI 0.20–0.95) during the post-transplant period. Steroids were weaned an average of 427 days (range 94 – 3519) after transplantation. The average number of episodes of high-grade rejection (ISHLT 3A/3B) within the first year was similar for patients maintained on steroids and for those weaned off steroids.

Conclusions: Treatment with a statin, an ARB, and steroid weaning were each associated with large mortality benefits. The mortality reductions demonstrated here warrant prospective study.

Ursodeoxyholic Acid for Chemoprevention in Ulcerative Colitis and Primary Sclerosing Cholangitis: A Retrospective Cohort Study. T. Ullman, L. Maratchi, V. Croog, D. Jaffe, and S. Itzkowitz. Dr. Henry D. Janowitz Division of Gastroenterology, Mount Sinai School of Medicine, New York, NY.

Background: Ulcerative colitis (UC) patients carry an increased risk of colorectal cancer (CRC). Patients with primary sclerosing cholangitis (PSC) and UC are at even greater risk. Animal models and two human reports have suggested that ursodeoxycholic acid (UDCA), a synthetic bile acid, may attenuate this risk.

Aim: To determine the effect of UDCA use on the development of colonic neoplasia (dysplasia or CRC) in patients with UC and PSC.

Methods: Following IRB approval, patients with both UC and PSC were identified by query of hospital medical records, outpatient records and the Mount Sinai GI pathology database. Medical, endoscopic, and surgical records of all such patients were then reviewed and abstracted for UC history, PSC history, UDCA dose and duration, colonoscopic surveillance history and outcomes. Life tables were constructed with diagnosis of PSC serving as t0 (time at which patients became available to take UDCA) and colonoscopy with flat low-grade dysplasia (LGD), high-grade dysplasia (HGD), or CRC serving as the primary outcome measure. Results were analyzed comparing UDCA users to non-users.

Results: We identified 50 patients with UC and PSC, 34 men and 16 women. Among them 32 were UDCA users (UDCA) and 18 were non-users (No UDCA). Mean duration of follow-up was 59.6 months, during which patients underwent an average of 2.1 colonoscopies (UDCA 2.1, No UDCA 2.0). During follow-up, 6 patients developed LGD (5 UDCA users, 1 No UDCA), 2 developed HGD (0 UDCA, 2 No UDCA), and 4 developed CRC (2 UDCA, 2 No UDCA). Actuarially, there was no difference in dysplasia development between the 2 groups; in univariate modeling UDCA users progressed at 0.70 the rate of non-users (95% CI, 0.23-2.17, $p=0.54$). After adjustment for duration and extent, the odds ratio decreased to 0.64, but was still not significant.

Conclusion: In our population of patients with UC and PSC, UDCA use offered little if any protection against the development of dysplasia. Careful surveillance or prophylactic colectomy is warranted in these patients.

Attempting to Reduce Inappropriate Vancomycin Use with a Computerized Reminder System. B. Metzger, A. Derevnuk, U. Conte, and D. Calfee. The Mount Sinai Medical Center, New York, NY.

Background: Vancomycin-resistant enterococci (VRE) are now responsible for over 25% of all enterococcal nosocomial infections in ICU patients and three cases of vancomycin-resistant *S. aureus*, each carrying the vanA gene from VRE, have been identified in the U.S. Antibiotic overuse is an important risk factor for the development of antimicrobial resistance. National recommendations for the use of vancomycin have been published by CDC-HICPAC but inappropriate use of this antibiotic continues.

Objective: To determine whether a computerized order entry system-based reminder that utilizes the CDC recommendations could reduce inappropriate use of intravenous vancomycin.

Methods: The Mount Sinai Hospital is a 1,000-bed urban teaching hospital. Baseline data on vancomycin use and its appropriateness were collected over a six-week period (Period 1) on three pilot inpatient wards. The same information was collected during a second six-week period (Period 2) following introduction of a computer-based reminder. During both periods, the medical record of patients receiving vancomycin for >96 hours was reviewed to determine the appropriateness of vancomycin therapy. During Period 2, if patients on the pilot wards received vancomycin for more than 72 hours, a summary of CDC recommendations for appropriate vancomycin use was displayed on the computerized order entry system. On this screen, the clinician was required to indicate if vancomycin would be discontinued or, if not discontinued, to select the appropriate indication for ongoing vancomycin administration. This screen persisted until a selection was made.

Results: During Period 1, 31 (38%) of 81 courses of vancomycin were continued longer than 96 hours. Of those, 14 (45%) were inappropriate. Among those 14, the mean duration of therapy was 7.0 days (median = 6.2 days). During Period 2, 36 (44%) of 81 courses of vancomycin were continued longer than 96 hours. Of those 36, 20 (56%) were inappropriate ($p=0.40$ vs. Period 1). Of those 20, the mean duration was 8.5 days (median = 6.25 days, $p=0.33$ vs. Period 1).

Conclusions: An intervention that used an existing computerized order entry system to remind clinicians of the CDC recommendations for appropriate vancomycin use was unsuccessful at reducing inappropriate vancomycin use and duration of therapy. Potential limitations of this type of intervention include a lack of a specific educational component and the absence of personal interactions between clinicians and antimicrobial stewardship program personnel.

Gram Negative Infections. G. Patel. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Gram negative infections are common causes of both morbidity and mortality in the hospital. An increasing percentage of these bacteria, especially *Escherichia coli* and *Klebsiella pneumoniae*, have developed extended-spectrum beta-lactamases (ESBL) that render them resistant to penicillins, cephalosporins, and aztreonam—the first line agents used to treat both nosocomial and community acquired infections. The goal of this study was to determine which patients are at risk for these infections and what clinical factors can be modified to reduce the prevalence of these resistant organisms at Mount Sinai Hospital. This is a retrospective analysis comparing the clinical parameters associated with gram negative infections and those associated with infections with gram negative ESBL producing bacteria. From May of 2001 to December of 2004 there were 109 documented cases of bacteremia caused by ESBL producing gram negative rods. Preliminary analysis indicates that prior antibiotic is a risk factor for these infections and there is some suggestion that liver disease, nursing home residence, and central venous catheters may also be risk factors.

Clinical Experience with Infliximab in the Treatment of Crohn's Disease at Mount Sinai. J. Potach. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Background: Infliximab (Remicade) is a chimeric monoclonal antibody against TNF-alpha given as intravenous infusion that has been shown to be effective in the treatment of Crohn's disease refractory to standard therapy. However the drug has been associated with many adverse effects, most notably acute and delayed infusion reactions occurring in as many as 15% of recipients. While there have been several randomized trials looking at the safety and efficacy of Infliximab, there is a paucity of data on the performance of the drug in non selected populations that are commonly encountered in clinical practice.

Methods: All patients over the age of 18 who received at least one dose of Infliximab for the treatment of Crohn's disease at The Mount Sinai Medical Center between October 1, 1998 and October 1, 2004 were eligible to participate. A comprehensive review of the patients' chart at the clinical infusion center was performed. Data were gathered on the number and schedule of infusions, dose, presence or absence of infusion reactions, treatment and prophylaxis of infusion reactions and ability to continue to receive Infliximab despite reactions. Following the chart review, patients were mailed two questionnaires. The questionnaires assessed for both response to therapy and the presence of adverse health events in the time period following infusion.

Results: A total of 318 patients received 1596 infusions during the study period. 98 patients (30.6%) had an infusion reaction. 79.5% of reactions were classified as acute or occurring within 24 hours of the infusion. The major symptoms were flushing, chest tightness and dyspnea. Only 0.5% of the infusions complicated by a reaction were unable to be completed after giving medications to alleviate the symptoms. There were no infusion related hospitalizations or deaths. However 40% of patients who had an infusion reaction did not receive additional therapy with Infliximab. The concurrent use of immunomodulating agents such as systemic corticosteroids and 6-mercaptopurine led to a non-significant trend in the reduction of infusion reactions. There was a non-significant decrease in the rate of infusion reactions in patients who were on fixed interval dosing schedules. Collection of data regarding efficacy of Infliximab and long-term adverse health effects is ongoing.

Conclusions: The use of Infliximab for Crohn's disease is safe. Although infusion reactions are common, they can almost always be treated and do not prevent the completion of the infusion. However infusion reactions may lead to decreased patient willingness to receive subsequent doses of the drug. The use of immunomodulating agents and fixed interval scheduling of doses leads to a non-significant reduction in infusion reactions.

Effects of HIV on Bone Mass in the Elderly. D. Restrepo[1], S. Jones[1], A. Kasowitz[1], D. Korenstein[1], S. Wallenstein[2], A. Schneider[1], and M. Keller[1]. Departments of [1]Medicine and [2]Biostatistics. Mount Sinai School of Medicine, New York, NY.

Background: Patients infected with HIV have experienced a dramatic decrease in morbidity and increase in life expectancy since the introduction of highly active anti-retroviral therapy (HAART). The advent of HAART coupled with effective prophylaxis for opportunistic infections has resulted in a dramatic increase in survival. As the HIV-infected population gets older, chronic illnesses are becoming an important part of HIV care. In parallel, there has been a progressive increase in the mean age of patients infected with HIV. 1–2% of newly diagnosed HIV disease occurs in individuals > 65 years of age and 10–15% involve patients > 50 years old. It is particularly important, in view of their near-normal lifespan, to examine the skeletons of elderly HIV patients who are already at high-risk for involutional osteoporosis.

The potential impact of chronic HIV infection on fracture risk began to receive attention after the report of two cases of low impact fractures and a case of osteonecrosis in young men with HIV who had been treated with HAART. Initial clinical and laboratory evidence suggests that HIV-infected patients with or without treatment may be at increased risk for osteoporosis. Antiretroviral side effects, prolonged exposure to HIV and/or activated immune cells are all possible causes for this observed association.The specific aim of this study is to compare a cohort of elderly HIV-positive females and males with matched HIV-negative controls to determine differences in bone mineral density and biochemical markers of bone turnover.

Methods: 64 HIV-infected and 64 HIV-negative subjects matched by age (within 2 years), sex and race are being recruited from the Infectious Disease and Internal Medicine clinics at the Mount Sinai School of

Medicine. Participants undergo a detailed medical and medication history, physical examination (including assessment of the body mass index and waist circumference) and dietary calcium intake survey at the General Clinical Research Center. Subjects with illnesses or medication use known to affect bone mass are excluded. Laboratory evaluation is performed in order to assess gonadal status, vitamin D levels, parathyroid function and bone turnover. Bone mineral density at the LS spine and femoral neck, instant vertebral assessment (IVA), and markers of bone turnover are being compared between the HIV-positive subjects and HIV-negative controls using the student's t test. Multivariate analysis will be used to control for known and potential confounders of bone mass.

Results: A total of 80 subjects have completed the study (48 HIV-positive cases and 32 HIV-negative controls. Of 17 matched pairs, the mean age is 60 years, 13 are female, and 4 are male. There are 9 Hispanics, 5 Blacks and 3 Whites. Among the HIV-infected subjects, 9 are on protease inhibitors and 8 are not. For the T and Z scores of the hip and spine, the cases have lower values than the controls and the differences are statistically significant.

Conclusions: Elderly women and men infected with HIV may have lower bone mass than age, race, and sex matched HIV-negative controls. Multiple regression analysis will be used to determine the relationship between bone mineral density and the viral load, CD4 count, duration of HIV infection, abdominal circumference and use and duration of specific classes of antiretroviral agents.

Intracoronary Stenting Prior to Non-cardiac Surgery. B.A. Sealove, R. Vilca, S.K. Sharma, M.C. Kim, and W.L. Duvall. Mount Sinai Medical Center, New York, NY.

Background: While percutaneous coronary intervention (PCI) is a commonly utilized risk-reduction strategy prior to non-cardiac surgery, concern has been raised regarding the safety of surgery in the six weeks following intracoronary stents due to stent thrombosis. The data predates the modern era of antithrombotic therapy used during PCI, and the outcomes of patients treated with GP IIb/IIIa inhibitors, clopidogrel, and heparin-coated stents are unknown.

Objective: To determine the clinical outcomes of patients at our institution who underwent non-cardiac surgery following PCI in the modern era of stent and antithrombotic therapy.

Methods: A total of 104 patients who underwent 108 non-cardiac surgeries were identified through the use of hospital billing records and the cardiac catheterization laboratory database at our institution. Over a three-year period (2000–2003), each patient had a pci within six months prior to a non-cardiac surgical procedure. Medical records were used to determine patients' antiplatelet and antithrombotic therapy as well as adverse cardiovascular outcomes seven and 30 days following surgery.

Results: Overall, 14 patients (13%) suffered an adverse event, with only one episode of stent thrombosis (0.92%). At 30 days post surgery, four patients had died (3.7%), one from cardiac causes (0.92%), six suffered a mi (5.6%), eight suffered cardiac ischemia (7.4%), three had repeat revascularization procedures (2.7%), and six had CHF (5.6%). Surgery occurred three to 180 days following PCI (median 45 days), with 47% of surgeries occurring within six weeks of PCI. There was no discernable pattern to the frequency of adverse events based on the duration of time from PCI to surgery (50% of the adverse events occurred within six weeks of PCI and 50% after six weeks).

Conclusions: The current study, performed during a more modern antithrombotic era, demonstrated no trend of increased adverse cardiac events in patients who underwent non-cardiac surgery soon after PCI. The rate of stent thrombosis was lower than in previously published reports (1.9% and 17.5%) and the overall mortality was comparable or lower (4.0% and 20%). This data suggests that with careful attention to antiplatelet therapy and more current stenting techniques, it may be safe to undergo non-cardiac surgery within six weeks of PCI. Further investigation using drug-eluting stents prior to non-cardiac surgery are underway.

How Well Do Health-Care Providers Recognize and Treat Sepsis in Hospitalized Patients? A.K. Sutherland, D. Nierman, and D.A. Kaufman. Mount Sinai School of Medicine, New York, NY.

Introduction: Sepsis is defined as a documented or suspected infection associated with signs of systemic inflammation. Severe sepsis is sepsis with evidence of organ dysfunction, and septic shock is sepsis with acute circulatory failure unexplained by other causes. These syndromes are prevalent among hospitalized patients, and cause a heavy burden upon society both in terms of loss of life and health care expenditures. A usual prodrome of sepsis is systemic inflammatory response syndrome (SIRS), which is characterized by abnormalities of at least two of the following values: temperature, heart rate, respiratory rate, or white blood cell count. In one study, 68% of patients admitted to 3 medical wards during a 9-month study period had SIRS. Of these patients, the prevalence of sepsis, severe sepsis and septic shock was 26%, 18% and 4%, respectively. The overall hospital mortality rate for patients with severe sepsis in 1995 was 28.6%, which accounted for 9.3% of all deaths in the U.S. that year. In an effort to improve outcomes for patients with sepsis, several international critical care medicine organizations formulated the Surviving Sepsis Campaign, publishing evidence-based guidelines for the diagnosis and care of patients with all stages of sepsis. These guidelines recommend the early identification and treatment of sepsis. In particular, based on the findings of a randomized controlled trial, the guidelines advocate early goal-directed therapy (EGDT), which is aimed at rapidly achieving normal circulation and perfusion.

Data from the Mount Sinai Hospital demonstrate that patients admitted to the medical ICU (MICU) from the hospital ward have a higher mortality rate than patients admitted from the Emergency Department. These data are consistent with findings from other investigators. Our anecdotal experience suggests that the diagnosis and treatment of sepsis is often delayed among patients on the hospital wards. Previous studies have associated delays in treatment with worse outcomes for critically ill patients. Other studies have associated delayed treatment of sepsis with worse outcomes.

As a quality assurance initiative, we sought to evaluate whether there are delays in the recognition and initiation of treatment of sepsis, severe sepsis and septic shock among hospitalized patients who required transfer from the general ward to the MICU. We looked at whether the treatments administered on the general hospital wards were consistent with the Surviving Sepsis Campaign guidelines. We chose to focus on sepsis, severe sepsis and septic shock both because of their prevalence and high rates of associated morbidity and mortality, and because there are now clear guidelines that can assist in measuring the timeliness and quality of care provided.

Methods: Two investigators screened all consecutive admissions to the MICU for patients who met 1991 Consensus Conference definitions for severe sepsis or septic shock at the time of MICU admission. We retrospectively reviewed the paper and electronic medical records of each patient with either severe sepsis or septic shock at the time of ICU admission. We noted all recorded vital signs, clinical events, clinicians' impressions and responses, and all laboratory abnormalities. We then reviewed each record to determine when clinicians diagnosed sepsis, severe sepsis or septic shock, what interventions they ordered and when consultation from the Critical Care Medicine service was requested. We then determined the timing of these diagnoses and interventions relative to the first clinical manifestation of sepsis, severe sepsis or septic shock and ICU admission. We also noted whether the treatments administered followed the evidence-based guidelines published by the Surviving Sepsis Campaign.

Specific Aims: This study was designed to observe caregivers' recognition of sepsis, severe sepsis or septic shock and their responses to the abnormal findings associated with these syndromes. Our observations are important in determining how best to focus the educational and patient care efforts of the Mount Sinai Hospital's MARS team. In addition, we plan to submit the findings of our study for presentation in abstract form at a national meeting and then submit our data for publication. By publicly sharing our data and observations, we hope to contribute to the international effort to improve outcomes for patients with sepsis by drawing attention to the quality of care provided for these critically ill patients.

Cardiovascular Disease and Modification of Traditional Cardiovascular Risk Factors in Early Chronic Kidney Disease: Data from the National Health and Nutrition Examination Survey, 1999-2000. C.M. Wyatt[1], Q. Xu[2], and R.R. Arons[2]. [1]Division of Nephrology, Mount Sinai School of Medicine, New York, NY, and [2]Mailman School of Public Health, Columbia University Medical Center, New York NY.

Context: Chronic kidney disease affects 10% of US adults, and individuals with early stages of chronic kidney disease are more likely to die of cardiovascular disease than to progress to end-stage renal disease.

Objective: This study investigates the prevalence of cardiovascular disease and cardiovascular risk factors, and the adequacy of risk factor modification among U.S. adults with early chronic kidney disease.

Design, Setting, and Patients: The National Health and Nutrition Examination Survey (1999 – 2000) provides nationally representative data on the heath status of the non-institutionalized civilian US population.

Main Outcome Measures: The prevalence of cardiovascular disease and cardiovascular risk factors was compared between stages of chronic kidney disease as defined by the National Kidney Foundation. The adequacy of risk factor modification was described among individuals with early chronic kidney disease (Stage 1 – 3).

Results: The prevalence of cardiovascular disease and traditional cardiovascular risk factors increases with increasing stage of chronic kidney disease. After adjusting for demographics and traditional cardiovascular risk factors, early chronic kidney disease remains associated with an increased risk of cardiovascular disease (OR 1.71, 95% CI 1.24 – 2.37), as well as an increased prevalence of hypertension (OR 1.90, 95% CI 1.42 – 2.55) and diabetes (OR 2.87, 95% CI 2.06 – 3.99). The association between early chronic kidney disease and cardiovascular disease, hypertension, and diabetes was not affected by the addition of hypoalbuminemia and elevated C-reactive protein to the model. Only 13% of US adults with early chronic kidney disease achieve combined goals for the management of hypertension, hypercholesterolemia, and diabetes.

Conclusions: Early chronic kidney disease is associated with a high prevalence of cardiovascular disease, even after adjusting for the increased prevalence of cardiovascular risk factors. Further studies are needed to elucidate novel risk factors and to determine the effect of improved cardiovascular risk modification on mortality and morbidity in this high-risk population.

Case Reports

End-Stage Liver Disease Is a Chronic Illness. T. Bishop. Mount Sinai School of Medicine, New York, NY.

End-stage liver disease is a chronic illness that is fatal if not treated with liver transplantation. Many patients experience chronic symptoms during the course of their disease. These symptoms include ascites, pain, confusion, dyspnea, peripheral edema. Other abnormalities that require long term management include hyponatremia, coagulopathies, and renal dysfunction. This article will review the current recommendations for managing long term symptoms in the cirrhotic patient.

Disseminated Histoplasmosis in Five Immunosuppressed Patients: Clinical, Diagnostic, and Therapeutic Perspectives. D. Caplivski, C. Salama, S. Huprikar, and E.J. Bottone. Division of Infectious Diseases, Mount Sinai Medical Center, New York, NY, and Elmhurst Hospital Center, New York, NY.

Objectives: Disseminated histoplasmosis is a relatively uncommon manifestation of a disease that primarily affects immunocompromised hosts. We reviewed five cases of disseminated histoplasmosis and examined the strategies that were used to establish a diagnosis in each case.

Methods: Five immunosuppressed patients (four with AIDS and one with a liver transplant) presented with fever, pancytopenia, elevated lactate dehydrogenase (LDH), and nodular pulmonary infiltrates (one miliary pattern). One patient had concomitant diffuse papular and purpuric skin lesions. All five originated from areas of Histoplasma endemicity (Puerto Rico, El Salvador, Brazil, and the Dominican Republic).

Results: While histoplasmosis was suspected clinically and epidemiologically, diagnosis was primarily achieved by visualization of phagocytosed Histoplasma yeast cells in peripheral blood smears, broncheoalveolar lavage, and in biopsy specimens. All four AIDS patients showed elevated urine Histoplasma antigen and LDH levels, whereas the liver transplant recipient had a false negative urine Histoplasma antigen and a normal LDH. With the exception of one AIDS patient (in whom diagnosis was delayed), all responded to induction therapy with amphotericin B followed by itraconazole.

Conclusions and Summary: Disseminated histoplasmosis should be suspected in immunosuppressed individuals who originate from areas of endemicity and present with pancytopenia, fevers, nodular infiltrates, and elevated LDH.

Prolonged Anticholinergic Toxicity after benztropine (Cogentin) Overdose: Case Report L.H. Pai. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Background: Benztropine mesylate (Cogentin) is an anticholingergic drug commonly used to lessen extrapyramidal symptoms in patients taking major tranquilizers and in those with Parkinson's disease. The abuse and overdose of benztropine is well reported in medical literature. However, physicians remain poorly aware of anti-cholingeric abuse. A case report of a 23-year-old woman who ingested benztropine in a suicide attempt is presented. Delirium and anti-cholinergic manifestations persisted for four days requiring prolonged hospitalization.

Case: A 23-year-old female with a history of depression was brought into the emergency room by her husband after being found confused, agitated, and hallucinating at home. A vial of her mother-in-law's beztropine tablets was found uncapped and empty at bedside. It was presumed that the patient had ingested her mother-in-law's benztropine in a suicide attempt. On admission patient was found confused, agitated, and mumbling incoherently. She had visual hallucinations and was persistently plucking at imaginary objects. She was not following or responding to any verbal commands. Vital signs, labs, ekg and head CT were unremarkable. On physical examination, pupils were dilated (5mm and sluggish) and mucous membranes were dry. A decision was made to not give activated charcoal secondary to aspiration risks and to monitor her on telemetry with a 1:1 observation. The first two days of hospitalization were characterized by agitation, active hallucinations, and combativeness. She also exhibited signs of psychomotor agitation, picking at her sheets. On the third day, she was more alert and oriented but continued to have disorganized thought process and was still delirious intermittently. On the fourth day, patient appeared more lucid. Patient recalled arriving at the hospital and acknowledged that she acted impulsively and regretted her actions. She was transferred to Psychiatry and discharged to home four days later.

Conclusion: Benztropine has been extensively used in this country, however, therapeutic serum benztropine concentrations are not defined. There have been no studies characterizing its pharmacokinetics. However, a long duration of effect is noted when using this agent. Benztropine overdose has been reported to persist for several days and is in keeping with the long duration of action that has been noted at therapeutic doses. Our experience in taking care of this patient also validate reported literature of long duration of effect of anticholingergic toxicity from benztropine overdose.

O1 and Non-O1 *Vibrio cholerae* Bacteremia Produced by Hemolytic Strains. D. Restrepo, S.S. Huprikar, K. VanHorn, and E.J. Bottone. Division of Infectious Diseases, Departments of [1]Medicine, [2]Pathology, and [3]Microbiology, The Mount Sinai Hospital, New York, NY.

Strains of *Vibrio cholerae* that agglutinate with antiserum O1 or O139 (O1 and O139) are the etiologic agents of cholera, a toxin-mediated acute diarrheal illness. Strains of *V. cholerae* that do not agglutinate in O1 or O139 antisera (non-O1) typically cause diarrheal illness mediated by toxins distinct from the cholera toxin. Although non-O1 *V. cholerae* bacteremia is fairly well described, *V. cholerae* O1 bacteremia is rare since this serogroup is not regarded as an invasive organism. In the summer of 2003 we observed two cases of *V. cholerae* (an O1 and a non-O1) bacteremia following diarrheal illnesses in immunocompromised patients with liver cirrhosis residing in New York City. In this report we describe their clinical presentation and conjecture that the hemolytic properties of the *Vibrio* isolates contributed to their ability to invade the bloodstream.

Health Services Research

Revascularization Decisions after Coronary Angiography at Mount Sinai Medical Center: A Survey. I. Nash[1] and C. Rahilly[2], [1]Cardiovascular Institute and [2]Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Objective: To elicit referring physicians' perceptions of their involvement in coronary revascularization decisions in patients whom they have referred for coronary angiography.

Background: Internists or non-interventional cardiologists referring their patients for coronary angiography have variable input into subsequent revascularization decisions. To our knowledge, no researcher at Mount Sinai or elsewhere has sought to elicit how involved referring doctors perceive themselves to be in coronary revascularization decisions in their patients.

Methods: We have developed a survey designed to procure referring physician's expectations regarding their involvement in revascularization decisions for their patients undergoing coronary angiography. Each member of Mount Sinai's Department of Medicine will receive a survey and an accompanying letter, asking for their voluntary participation in the survey. The survey consists of some initial questions requesting information regarding specialty training and volume of patients referred to Mount Sinai's cardiac catheterization laboratory for coronary angiography. Remaining questions seek to elicit referring doctors' perceptions of their involvement in revascularization decisions in their patients whom they have referred for coronary angiography, and what process by which such physicians would prefer such decisions are made. The survey is anonymous, and responses will not be identifiable to participants.

Analysis: The results of the survey will be summated and presented in a qualitative fashion. Analysis will determine the frequency by which one process versus another is us used to make revascularization decisions (such as the interventional cardiologist making revascularization decisions at the time of the angiogram, versus discussing the findings of the angiogram with a referring internist first), according to perceptions of referring physicians. Analysis will also determine whether the process by which revascularization decisions are made reflect what referring physicians consider the "best" process for making such decisions.

Public Health / Epidemiology Research

Senior Citizen Travel: An Analysis of the Geosentinel (GeoS) Surveillance Network. K.D. Sigel[1], G. Rosselot[1], L. Weld[2], P. Pandey[3], M. Schunk[4], B. Connor[5], M. Shaw[6] and A. Gurtman[1], for the Geosentinel Surveillance Group. [1]Department of Medicine, Mount Sinai School of Medicine, New York , NY, [2]Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, Atlanta, GA, [3]CIWEC Clinic Travel Medicine Center, Kathmandu, Nepal, [4]University of Munich, Munich, Germany, [5]Weill Medical College of Cornell University, New York , NY, and [6]Worldwise Travellers Health and Vaccination Centre, New Zealand.

Objectives: There is a dearth of literature examining travel related illness in the elderly population. The purpose of this study is to determine demographic and clinical characteristics of elderly travelers, by utilizing data collected at Geosentinel surveillance network clinics.

Methods: The population studied was all Geosentinel travelers aged 65 and older (excluding those with only immigration as a reason for travel). The comparison group was all Geosentinel travelers aged 25–44. Univariate and multivariate analyses were performed to determine differences in demographics, diagnoses, and clinical presentation amongst the comparison groups. Statistical significance was determined with chi-squared and logistic regression analyses.

Results: A total of 1,201 travelers aged 65 and older were included in the analysis, as well as 16,542 travelers aged 25 through 44, as a comparison group. The elderly travelers in the GeoS database were primarily traveling for tourism, and were significantly less likely to have had a pretravel encounter than their younger counterparts. (50% vs. 65%, $p<0.001$) The most common diagnoses were similar amongst the two groups, with respiratory infections and acute diarrhea being very common. The older travelers presented significantly less acute diarrhea than the younger travelers (22% vs. 14%, $p<0.01$) and more respiratory illnesses (10% vs. 14%, $p<0.01$), and their respiratory illnesses appear to have been more severe. The elderly travelers were significantly more likely to present after travel with a dermatologic, cardiac, or respiratory chief complaint, and were less likely to present with gastrointestinal, fever-related, ENT-related, genitourinary, or fatigue-related chief complaint. Elderly GeoS travelers with acute diarrhea were significantly more likely to present with a cardiac complaint, (OR 5.1, $p=0.02$), or a respiratory complaint (OR 2, $p=0.03$) than younger GeoS travelers with acute diarrheal illness. Elderly travelers with diarrhea were significantly more likely to have traveled to South America (OR 2, $p=0.04$) and South Central Asia (OR 2.23, p(0.01), than elderly travelers without diarrhea. Elderly travelers with STD's were much more likely to have traveled to SE Asia (OR 3.6, $p=0.05$) than other travelers aged 65 and older without STD diagnoses, and those with malaria were much more likely to have traveled to sub-Saharan Africa (OR 6.4, $p=0.01$) than elderly travelers without malaria.

Conclusions: Elderly travelers in the GeoS have many of the same illnesses as their younger counterparts, but present with a different spectrum of complaints, and amongst their different diagnoses exhibit different patterns of travel.

Translational Research

Seminal Fluid Proteins Interfere with the Anti-HSV Activity of Candidate Microbicides in Clinical Development. S. Patel[1*], M. Keller[1], K. Hogarthy[1], A. Tuyama[2], M.J. Carlucci[2], E. Fam[2] and B.C. Herold[2]. Departments of [1]Medicine and [2]Pediatrics, Mount Sinai School of Medicine, New York, NY. (*SP is a Doris Duke Medical Student Scholar)

Introduction: Currently there are over 40 million people living with HIV/AIDS; heterosexual transmission accounts for the majority of new cases. This epidemic is fueled by a parallel epidemic of genital herpes infection. Epidemiological studies demonstrate that HSV infection increases the risk of HIV acquisition and that co-infection with HIV and HSV increases both HIV transmission and replication. Current options are limited to condom use, which is often difficult for women to negotiate. Therefore, the development of topical microbicides, compounds designed for vaginal application to prevent acquisition and transmission of HIV and HSV, is a major health priority. Microbicides currently in Phase II/III clinical trial include several polyanion compounds that bind to the viral glycoproteins gp120 of HIV and gB of HSV-2 to block binding and entry. These compounds inhibit HIV and HSV in cell culture, organ explants and animal models. However, while their activity is preserved in the presence of cervicovaginal secretions and over a broad pH range, no study has assessed the anti-viral activity if virus is introduced in seminal fluid. Seminal fluid is alkaline and contains ~25 mg/mL protein, many of which are unique to semen. The purpose of this study is to test the anti-HSV activity of candidate microbicides if virus is introduced in the presence of seminal fluid using cell culture assays and a murine model.

Methods: Clinical specimens were obtained from healthy individuals, ages 18–50, after obtaining informed consent. HSV plaques assays were performed on human cervical epithelial (CaSki) cells. Microbicides evaluated included PRO 2000, a sulfonated napthalene compound currently in two large-scale Phase II/III trials, SAMMA, a non-sulfonated anionic mandelic acid, and SpM8CHAS, a sulfonated amphiphilic umbrella compound. Cells were pre-treated for 1 hour at 37°C with one of the three compounds diluted in PBS or cervicovaginal lavage fluid (CVL). HSV-2 isolates were then introduced in PBS, seminal plasma, or a control HEPES buffer adjusted to the pH and protein concentration of seminal plasma. The cells were again incubated for 1 h at 37°C. Infection was monitored by counting plaques at 48 h. For murine studies, mice were pretreated with a single dose of medroxyprogesterone 5 days prior to application of formulated PRO2000 and then challenged 15 min later with virus diluted in PBS or seminal fluid. Mice were monitored for signs and symptoms of genital herpes and sacrificed if significant genital ulcers or neurological disease developed.

Results: There was a significant and substantial loss of anti-HSV activity for PRO 2000 (unformulated and formulated drug) and SAMMA if virus were introduced diluted in seminal fluid compared to matched control buffer or PBS. The anti-viral activity of Spm8CHAS was also reduced, but to a lesser extent. The interference observed with seminal fluid persisted in the presence of CVL, which itself has intrinsic anti-HSV activity. A fluorescence assay, which measures free PRO 2000, indicates that seminal proteins, but not albumin, bind PRO 2000. In contrast, blood serum proteins did not interfere with microbicide activity, suggesting that a unique seminal fluid protein(s) mediated the interfering activity. Fractionation studies using Centricon preps indicated that the interfering proteins are higher molecular weight (~100kD). Mass spectrophotometry studies are ongoing to identify proteins in this fraction. Preliminary murine studies suggest that the interference observed *in vitro* translates to a reduction in effectiveness *in vivo*; PRO 2000 2% gel protects 80 % (4/5) mice if virus is introduced in PBS but only 40% (2/5) mice if virus is introduced in seminal plasma.

Conclusion: These studies demonstrate that high molecular weight protein(s) found in seminal fluid bind to anionic microbicides reducing their effectiveness in cell culture and in a murine model. If validated in ongoing human clinical trials, identifying the interfering protein(s) and mechanism of action should facilitate development of formulations to overcome this phenomenon.

Jersey City Medical Center

The Effect of Moving to a New Hospital on the Prevalence of Resistant Bacteria. C. Tadros[1], R. Guerrero[2], A. Gregoriu[1], and C. Strand[2]. Departments of [1]Medicine and [2]Pathology. Jersey City Medical Center, Jersey City, NJ.

Introduction: The influence of hospital design on nosocomial transmission of resistant bacteria has not been formally studied. Our hospital's relocation in May 2004 to a new building, with new and different ward and ICU designs, prompted us to study the antimicrobial susceptibility patterns in the new vs. the old hospital.

Method: The method used is a laboratory information system search of patient results with determination of cumulative susceptibility of pathogens recovered from inpatients and outpatients in the new vs. the old hospital. The study examines these patients' antibiograms over a 12-month period, before the move, and in the 9-month period after the relocation. Only data for organisms with more than 10 isolates is included. The study follows the CLSI guidelines for antibiograms using only first isolates per patient per stay.

Results: The gram-positive organisms was found to have no significance in susceptibility pattern in the old vs. new hospital. However, for the gram-negative organisms, *A. baumannii* was more susceptible to Amikacin and Imipenem in the new vs. the old one. The other common gram-negative bacteria showed no significant difference.

Conclusion: Radical facility design changes, which enhance optimal infection control practices, in our study led to a significant improvement in sensitivity of *A. baumannii*. However, the data show no change in the prevalence of resistance in other gram-negative or gram-positive bacteria.

Comparison of Antimicrobial Resistance Patterns of Three Hospitals. M. Fernandez[1], R. Guerrero[2], L. Vaccaro[3] A. Grigoriu[1]; C. Strand[2] N. Go[1], R. Munera[2], S. Nayak[2], and A. Khan[2]. Departments of [1]Medicine, [2]Pathology and [3]Infection Control. Jersey City Medical Center, Jersey City, NJ.

Introduction: The antimicrobial susceptibility patterns from the three LibertyHealth hospitals were evaluated by analyzing retrospectively each hospital's antibiogram over a two-year period.

Objective: To compare resistance patterns of three hospitals belonging to one hospital system located in Hudson County, NJ.

Method: The antimicrobial susceptibility testing followed standard guidelines using the Vitek 2.

Results: The results showed narrow range of susceptibility (44–54%) for methicillin resistant *Staphylococcus aureus* in the 3 hospitals. *Enterococcus faecalis* susceptibility rates to ampicillin were similar (97–100%) as well as for vancomycin (88–92%). *Escherichia coli* was the most common gram-negative isolate in all 3 hospitals, followed by *Pseudomonas aeruginosa*. The ampicillin sensitivities of *E. coli* were in Jersey City Medical Center (JCMC) (42%) Meadowlands Hospital (MH) (53%) and Greenville Hospital (GH) (37%) and the Trimethopin/Sulfa susceptibilities were also comparable (65–71%). *P. aeruginosa* susceptibilities to cefepime varies: JCMC (44%), MH (33%) & GH (57%); ceftazidime susceptibilities were JCMC (44%), MH (64%) & GH (57%). *Acinetobacter baumannii* was a common isolate and was highly resistant to ampicillin/sulbactam at JCMC (48%), MH (61%) & GH (58%) as well as to amikacin at JCMC (44%), MH (42%) & GH (44%).

Conclusion: There are important differences in prevalence and antimicrobial susceptibility patterns of the Gram-positive bacteria and Gram-negative bacteria isolated from the three hospitals. This strongly suggests multiple mechanisms of resistance.

Knowledge of Medical Residents about Hospice and Palliative Care: A Brief Survey. S. Hosadurga, H.D. Park, X. Mdluli, J. Shah, T. Borisiak, and M. Reisner. Department of Medicine. Jersey City Medical Center, Jersey City, NJ.

Background: Palliative and hospice care has become a more essential element of patient care as the aging population increases. In November 2004, a brief survey was done for the 32 internal medicine residents at Jersey City Medical Center regarding knowledge about palliative and hospice care.

Results: 94% of residents have no experience of hospice care outside of the hospital setting. 85% of residents did not clearly understand the composition of core hospice team. 66% of residents showed lack of knowledge about the continuation of hospice benefits after patient is deceased. 60% of residents misunderstood the role of PED tube for the hospice patient.

Conclusion: This study demonstrated fundamental lack of knowledge about hospice and end-of-life care among the medical residents. As the aging population increases, education for hospice and end-of-life care should be prioritized.

The Pathogen Microoganisms Frequency and Antibiogram in Jersey City Medical Center New Neonatal Intensive Care Unit (NICU) as Compared to the Old NICU. J. Padilla[1], P. Patel[1], S. Umaru[1], C. Strand[2], S. Alsheikh[1], S. Puvabanditsin[1], and R. Guerrero[2]. Departments of [1]Medicine and [2]Pathology. Jersey City Medical Center, Jersey City, NJ.

We studied the frequency of specific microorganisms and antimicrobial susceptibility of the first isolates as recommended by the NCCLS for the Jersey City Medical Center old NICU (1/2002–5/16/2005: 28 months) vs. the new NICU (5/2004–2/2005: 8 1/2 months). The study data shows that coagulase negative Staphylococcus (CNS) is the leading cause of sepsis in both periods/unit representing 47% (old) and 36% (new) of the total isolates (81 and 66). There is an increase in isolation of *Staphylococcus aureus* in our new NICU, it represents 29% of the isolates compared to 15% in our old NICU. *Pseudomonas aeruginosa* represents 18% (new) and 12% (old) followed by *Escherichia coli* 11% (new) and 13% (old); *Serratia marcescens* 6% (new) and 10% (old).

Important observations based on this data are: (a) Oxacillin sensitive coagulase negative Staphyllococcus is 14% in our new NICU compared to nil in our old NICU; (b) Oxacillin-sensitive *S. aureus* are 79% (old) and 68% (new) isolates. There is a spike increase in methicillin-resistant *S. aureus* (MRSA) in our NICU; (c) Gentamicin-sensitive *P. aeruginosa* is 92% in the new NICU compared to 78% in our old NICU. (d) Gentamicin/Tobramycin-sensitive *E. coli* is 71 % in our new NICU compared to 100% in our old NICU.

Emergent Chemotherapy as a Modality of Treatment for Symptom Reduction in Massive Hemoptysis from Small Cell Carcinoma Impinging on the Left Atrium and Pulmonary Veins. R. Dharmaji, P. Venkataswamy, A. Reddy, H.D. Park, and J. Matta. Department of Medicine. Jersey City Medical Center, Jersey City, NJ.

Learning Objectives: Recognize hemoptysis as a presenting sign of small cell carcinoma metastasizing to left atrium and pulmonary veins. Recall that emergent chemotherapy has a role in symptom reduction.

Case: A 41-year-old African-American male with no prior medical history, who smoked one pack per day for more than 15 years, comes with chief complaint of cough with blood streaked sputum for 2–3 days, which transforms into a full-blown hemoptysis within few hours of admission. Initial bronchoscopy showed massive hemoptysis, the exact source of bleeding could not be visualized. Emergent arteriogram for embolectomy to arrest the bleeding site was unsuccessful. CT chest showed a 4×5 cm irregular mass abutting the left atrium and the pulmonary veins. Patient underwent open lung biopsy and the frozen section of the specimen was identified as a small cell carcinoma, which later was confirmed by the pathologist. Emergent chemotherapy with cisplatin given for three days resulted in complete stoppage of hemoptysis with rapid recovery and resulting in extubation.

Discussion: Emergent chemotherapy has a role in the tumor shrinkage resulting in reduced risk of hemoptysis. In one review (1997), mesothelioma, melanoma, lung cancer and renal neoplasms were most likely to metastasize to the heart. Among lung cancer, anaplastic small cell and adenocarcinoma showed the most frequent heart involvement in males, while squamous cell carcinoma was more common in females. Our patient, who had small cell carcinoma, responded well to emergent chemotherapy resulting in tumor shrinkage.

Markedly Elevated CA-19-9, Does Not Always Indicate Pancreatic Cancer. S. Soosaimanickam, C. Valle, M. Koehn, P. Thiruvilwamala, R. Chinai, and P. Weissman. Department of Medicine. Jersey City Medical Center, Jersey City, NJ.

Introduction: The tumor marker CA 19-9 is based on monoclonal antibody to colonic carcinoma cell lines. CA 19-9 is expressed in pancreatic carcinomas. It is also found in normal pancreas and in chronic pancreatitis. Here is a case of pancreatic disease where CA 19-9 was marked elevated and yet proved to be a benign lesion.

Case: A 33-year-old male with no medical history presented with acute right upper quadrant pain and jaundice. He was ruled out for Hepatitis A, B, C, HIV and for Tylenol overdose. Denied alcohol abuse. Total bilirubin from 10 to17, direct bilirubin from 6.5 to 11 and alkaline phosphates from 350 to 636. Jaundice was consistent with obstructive pattern. Ultrasound abdomen-sludge in gall bladder, no stones or dilatation of common bile duct (CBD). CT–dilated gall bladder, no pancreatic mass. AFP-3, CEA-3.2, CA 19-9(437452 U/mL, (Normal <37 U/mL), PTCA revealed filling defect in distal CBD possible stone or stricture. He underwent exploratory laparotomy, cholecystectomy, CBD exploration, choledochoscopy and pancreatic head biopsy. CA 19-9 decreased to 1856 and then to 205 U/mL. Biopsy revealed fibrosis of peripancreatic tissue and chronic inflammation of CBD, gall bladder. Pancreatic malignancy and cholangiocarcinoma were ruled out. Although CA 19-9 was markedly elevated, further evaluation showed it was due to benign stricture.

Conclusion: CA 19-9 may be elevated in both benign as well as malignant conditions and interpretation of CA 19-9 results must be made in light of clinical condition.

Hyperthyroidism as the Cause of Cholestatic Liver Disease. C. Castillo, M. Sethi, and R. Rojas. Department of Medicine. Jersey City Medical Center, Jersey City, NJ.

Case: A 47-year-old male who presents with one month history of jaundice, generalized pruritus, trouble sleeping, tremors, weight loss (30 lbs.), diarrhea and abdominal pain. Past medical history is not relevant. Social history of alcoholism, last alcohol intake one year before admission. Alkaline phosphatase 309 IU/L, ALT 112 IU/L, AST 161 IU/L, bilirubin direct 1.0 mg/dl and bilirubin total 1.4 mg/dL. Renal function is normal. Abdominal ultrasound, CT scan of abdomen, and MRCP are unremarkable. Hepatitis profile, HIV test, ANA, antimitochondrial antibody and antismooth antibody are negative. There is no heart failure. Thyroid function test: TSH: 0.02 UIU/mL, T4: 19.80 UG/dL, T3: 411.7 ng/dL. The patient was treated with iodine I-131: (20.9 mCi) orally. Two months later liver function tests are almost back to normal, the patient is gaining weight and admits to being asymptomatic.

Discussion: One of the many hepatic functions is the metabolism of the thyroid hormones. Therefore, it can be expected that the alterations of thyroid hormones influence hepatic function with different intensity, depending on the individual characteristic (in the case history of alcohol abuse). This case emphasizes that hyperthyroidism should be consider in the differential diagnosis of cholestasis.

An Unusual Presentation of a Common AIDS Related Condition. M. Fernandez[1], C. Castillo[1], A. Grigoriu[1], D. Flores[1], C. Strand[2]; U. Pai[2], and H. Upadhyaya[1]. Departments of [1]Medicine and [2]Pathology. Jersey City Medical Center, Jersey City, NJ.

Introduction: Kaposi's Sarcoma (KS) is a malignant skin lesion seen before 1980 in elderly white men and now in homosexual men with AIDS. The Human Herpes virus 8 (HHV-*) is universally present in all forms of KS.

Case: A 36-year-old male presented to Infection Disease Clinic with swelling, tenderness, and redness of the right knee. He had a history of HIV/AIDS, CS4 (40) viral load of 191,250 copies and noncompliance with highly active antiretroviral treatment (HAART) medications. He also had a history of oral thrush, MAI and chronic pancreatitis. He denied prior history of knee trauma, no sexual relations, no IV drug use, no history of gout, Lupus or rheumatoid arthritis. Vitals were blood pressure 125/72, P 82, RR 18, T 98.&. Right knee showed swelling, redness and mild limitation of movement; the rest of the exam was normal. X-ray of right knee showed only degenerative changes; a venous Doppler was negative for deep vein thrombosis (DVT), but revealed external compression of right popliteal vein due to cutaneous inflammatory lesions. He received Ultram for pain and HAART medications. One week later the patient came back with more pain in the right knee and described a tingling, burning sensation starting from the right groin area, coming down to the calf. There were vesicular lesions of the right medial knee in a dermatomal pattern. Valtrex was given and a few days later the lesions were transformed to furunculated masses that spread to the groins area. The leg was very swollen; he as not able to walk and was sent to the hospital. Surgical biopsy of the lesion revealed KS, and the patient improved rapidly with chemotherapy.

HIV 1 ITP in Hepatitis C. P. Thiruwilwamala and A. Grigoriu. Department of Medicine. Jersey City Medical Center, Jersey City, NJ.

Introduction: Immune thrombocytopenic purpura is seen in approximately 40% of HIV infection patients (HIV-1-ITP). Destruction of platelets mediated by antiplatelet antibodies and/or platelet bound immune complexes is also seen in hepatitis C infection.

Case: 37-year-old woman with HIV and hepatitis C co-infection who presented with thrombocytopenia. Patient had multiple hospital admissions for symptoms of epistaxis, bleeding per rectum and skin petechiae. Her baseline platelet counts were 2K-5K. Diagnostic workup including bone marrow biopsy and antiplatelet antibody proved ITP. She failed several attempts of treatment with steroids, IV immunoglobulin and AntiD. Rituximab and splenectomy were deferred in view of poor outcome. In the past, this patient was also noncompliant with highly active antiretroviral treatment (HAART) medications, had an episode of PCP pneumonia, genital herpes and had a short course of Peginterferon for hepatitis C.

Discussion: Recognition of ITP in HIV-hepatitis C co-infected patients is important. The autoimmune nature of the disease, associated with hepatitis C and advantage of HAART in improving platelet counts should be kept in mind in addition to the first line of treatment. Cause of secondary thrombocytopenia including medications and viral/bacterial infections are also significant.

Miliary Tuberculosis as a Source of Puerperal Fever. H.D. Park, D. Kim, X. Mdluli, and L. Tacsa. Department of Medicine. Jersey City Medical Center, Jersey City, NJ.

Learning Objectives: (a) To distinguish fulminant form of miliary tuberculosis from other forms of acquired pneumonia. (b) To identify effective diagnostic approach to disseminated tuberculosis

Case: A 34-year-old Indian female living in the U.S. for 9 years with no known prenatal care presented with fever and productive cough one day after pre-term delivery. Physical examination findings showed occasional rhonchi in the chest. Chest X-ray and CT scan revealed bilateral diffuse reticulonodular infiltration involving both lower lobes. Despite empiric antibiotics treatment for 9 days, there was no clinical improvement. All the cultures and HIV test were negative. PPD showed 20 mm of induration. Laboratory data showed chronic anemia and elevated alkaline phosphatase. Liver, transbronchial and bone marrow biopsies revealed necrotizing and non-necrotizing granulmomas that were consistent with disseminated tuberculosis. The condition of the patient has improved after starting anti-tuberculosis treatment. The patient was discharged on the 36th post-delivery day.

Discussion: Miliary tuberculosis is an important differential diagnosis to the pneumonia patient who does not respond to conventional antibiotics, especially in the immigrant population group. Liver biopsy reveals highest yield among all the tissue diagnostic modalities in diagnosing disseminated tuberculosis.

Streptococcus Pneumoniae Meningitis Presenting as Altered Mental Status. Z. Awan, H. Moghaddam, A. Devarajan, and J. Matta. Department of Medicine. Jersey City Medical Center, Jersey City, NJ.

Learning Objectives: (a) Consider *Streptococcus pneumoniae* as a caustic organism for meningitis in patients with altered mental status. (b) Even if the CSF is negative for any organisms, with positive blood cultures for *S. pneumoniae*, consider treating meningitis as due to *S. pneumoniae*.

Case: A 57-year-old African-American female with h/o HTN evaluated for acture onset of altered mental status. Patient complained of severe headache with blurry vision the previous day and found to have drowsiness, lethargy, incoherent talk, feverishness, stiff neck, urinary incontinence without nausea and vomiting. Exam revealed an agitated, confused female, temp of 103°F, no neurology deficit except for a stiff neck, CT scan of head was negative, XCR was normal. Lumbar puncture revealed cloudy colorless CSV, glucose: 29; protein: 413, India ink -ve, WBC: 3650; (P-36, L-4), RBC: 4,200, gram stain and culture negative for any organism, bacterial antigen for *S. pneumonia* +ve, CBC showed WBC 20.4, glucose 260, blood for gram stain showed G+ve cocci in chains and culture isolate *S. pneumoniae*. Patient was initially intubated for airway protection, treated with Pocephin and Dexamethasone. Patient regained full consciousness on the 3rd day and extubated.

Discussion: Early consideration of *S. pneumoniae* meningitis with early institution of appropriate antibiotics and Dexamethasone results in rapid return of consciousness with no neurological sequelae. Even though CSF did not reveal organisms, isolation of organism in the blood is sufficient basis for effect treatment.

The Effect of Intravenous Immunoglobulin (IVIG) in the Treatment of Toxic Epidermal Necrolysis. Varadarajan, P. Venkataswamy, and R. Mikkilineni. Department of Medicine. Jersey City Medical Center, Jersey City, NJ.

Introduction: Toxic epidermal necrolysis (TEN) is a severe cutaneous reaction mostly secondary to drugs, with high morbidity and mortality rate.

Case: A 23-year-old Hispanic male was transferred to the hospital as he developed a diffuse rash all over his body. He developed sore throat about 3 days prior and took one unknown pill from a fellow inmate at 7 PM the previous night. At about 1 AM he noticed the rashes on his trunk, his face and then his extremities. It was getting worse over the day, accompanied by ulcers in the mouth and he was transferred to the ER. About 6 months prior, patient developed similar rash following penicillin ingestion and was hospitalized for 3 weeks with a diagnosis of Steven Johnson syndrome, for which he did not receive IVIG. On physical exam he was a moderately built male with polymorphic rashes ranging from small erythematous papules, palpable purpurae to 2–3 ringed target lesions, some with central vesicles were present all over the body, involving about 70% of the body surface area. We started him on IVIG within 24 hours of onset of rash and continued for 4 days. Over the next day the size of the lesions halted, but became more bullous and he had an episode of epistaxis with serosanguinous fluid. Nikolsky's sign was present. Patient felt significantly better earlier than the previous episode and was discharged in 10 days rather than 3 weeks.

Conclusion: Controversies still exist about the use of IVIG in the treatment of TEN. In our case, early administration of IVIG did significantly reduce the morbidity in terms of subjective symptoms and length of stay. IVIG may be beneficial compared to supportive care when administered early in the course of treatment of TEN.

A 30-Year-Old Male with Single Ventricle Presenting with Bradyarrhythmia. E. Bacorro, P. Thiruwilwamala, and J. Javed. Department of Medicine. Jersey City Medical Center, Jersey City, NJ.

Introduction: Single ventricle is a rare congenital anomaly which presents at birth with cyanosis, congestive heart failure (CHF), or both. Palliative surgery is generally required early in life.

Case: A 30-year-old male with history of diabetes mellitus, intravenous drug abuse (IVD)A, and congenital heart disease (CHD) was brought to the ER due to chest pain, palpitations, dizziness and shortness of breath. Examination revealed an irregular heart rate, with systolic murmur at precordial area. EKG showed sinus rhythm, 1° AV block, and Q and ST changes in II, III, AVF. He had occasional junctional rhythm with the PVcs on telemetry. Echocardiogram showed a single ventricle with a graft occluding the AV valve. He was transferred to CCU and stabilized. During childhood, he was diagnosed to have a single ventricle, LV type, with severe valvular and supravalvular pulmonary stenosis. At 18 years old, he had a modified Fontan-Kreutzer repair, with closure of the right atrioventricular valve and anastomosis of the main pulmonary artery to the roof of the right atrium. He was apparently well afterwards. However, since 2003, he had various admissions for CHF, atrial fibrillation/flutter, digoxin toxicity, and bacterial endocarditis.

Conclusion: Although patients with CHD are seen by pediatric cardiologists and surgeons, improvements and modifications in surgery have resulted in long-term survival and improve quality of life. Consequently, these patients are increasingly seen by adult medicine specialists. It is therefore important for internists to be familiar with the sequelae and associated complications of the surgical procedures, and the management of these conditions.

Benefits of Thrombolytic Therapy in Massive Pulmonary Embolism. E. Martinez, S. Titapiwatanakun, C. Onunkwo, M. Sethi, T. Borisiak, and D. Flores. Department of Medicine. Jersey City Medical Center, Jersey City, NJ.

Case: A 32-year-old African-American male with history of complicated diabetes mellitus admitted with sudden onset of shortness of breath (SOB). Time since onset of symptoms to ER was 2 hrs. On admission patient was in severe respiratory distress – RR 40, diaphoretic, hemodynamically unstable (hypotensive, tachycardic, hypoxemic) that supported decision of intubation. Labs: D-dimer – 9.41, arterial pOx – 163 on 100% NR mask. CKMB – 4.6, trop – 0.5. Patient was administered levophed, insulin and heparin ggt. Lower extremity venous US showed CVT in left common femoral and popliteal veins. ECHO – decreased RVF, dilated, RV. V/Q scan – massive left lung pulmonary embolus with no perfusion. Decision was made to administer TPA 100 mg. Without change in heparin ggt (PTT $2^{1}/_{2}$ NL value). In less than 12 hours after TPS administration patient regained hemodynamical stability, arterial PO2 normalized and follow-up V/Q scan showed completed resolution of pulmonary embolism.

Discussion: Right-sided heart failure and recurrent pulmonary embolism are the main cause of death associated with pulmonary embolism in the first two weeks after the embolic event. Indications for thrombolysis are not well defined and thus controversial. The only current absolute indication is massive pulmonary embolism with hypotension, which was the clinical scenario with our patient. Other potential indications include right heart dysfunction, recurrent pulmonary embolism and the prevention of pulmonary hypertension. However, no evidence exists to show benefit of thrombolytic therapy over standard anticoagulation therapy for recurrent pulmonary embolism, mortality or chronic complications. Bleeding is the most common complication of thrombolysis and may be fatal.

Queens Hospital Center

When Wheezing Is Not Due to Asthma. K. Amaechi, E. Okundaye, D. Reich, and R Lopez. Queens Hospital Center, Mount Sinai Services, Jamaica, NY.

We report the case of an elderly woman with multiple hospitalizations for illness, which in the past had been variously diagnosed as asthma, congestive heart failure, and pneumonia. The patient's symptomatology appeared not to fit into any one specific disease category in this, as in previous admissions. Her present illness proved to be another great mimicker in medicine and her response to a variety of treatments remained suboptimal until the proper diagnosis was made, given a careful clinical assessment of her illness.

Case Report: PM is an 80-year-old woman who presented with complaints of shortness of breath and cough that produced clear sputum for two weeks with occasional bloody streaks. She had progressive shortness of breath, orthopnea and leg swelling, but denied fever. She had been diagnosed with late-onset asthma during a previous admission, had well-controlled diabetes, and never smoked nor used illicit drugs. She had retired from her job of making artificial hair for dolls 15 years earlier. Review of systems was significant for weight loss of 10 lbs over a one-month period. The patient's medications were fosinopril, metoprolol, rosiglitazone, furosemide, albuterol and ipratropium metered dose inhalers. Physical examination revealed an afebrile, dyspneic and wheezing woman. On ausculation, she had ronchi in both upper lung zones and crepitations in both lower zones. The extremities were significant for grade one, non-pitting pedal edema. The white blood cell count, serum chemistries and chest X-ray were normal, and two sets of blood cultures were did not grow any organisims after five days.

Her present illness was treated as an exacerbation of asthma and chronic heart failure. While this patient was receiving nebulizers and diuretics her pedal edema improved, however, she continued to feel generally weak and she deteriorated despite therapy, with persistent cough and shortness of breath. An echocardiogram was subsequently obtained, which revealed a left ventricular hypertrophy, a normal ejection fraction, a Tajik grade one diastolic dysfunction and a pulmonary artery systolic pressure of 33 mmHg. The echocardiographic findings failed to account fully for the patient's collection of signs and symptoms, and some other pulmonary etiology was suspected.

At this point, the dose of diuretics was gradually reduced, and further testing pursued. Pulmonary function tests (PFT) and high-resolution computed tomography (HRCT) of the chest were obtained. The PFT study was limited due to poor patient effort and fatigue, however data obtained was sufficient to suggest a restrictive ventilatory defect. HRCT of the chest revealed bilateral bronchiectasis with extensive fibrotic changes in the lung bases. In the light of this finding antibiotics were then added to the treatment regimen, and the patient demonstrated marked improvement of her symptoms.

Discussion: Bronchiectasis is defined as an abnormal and permanent dilatation of bronchi and bronchioles. The diagnosis requires a high clinical suspicion and the gold standard for its diagnosis is a HRCT. Patients with bronchiectasis frequently have recurrent infections, with increased secretions that can harbor pathogens. Inflammatory mediators are released, and these together with bacterial activity lead to destructive changes in the bronchial wall, squamous metaplasia, and increased vascularity of the bronchial vessels culminating in fibrous tissue replacement. Common causes include pneumonia, TB, HIV, endobronchial tumors, cigarette smoking, recurrent gastric aspiration, hereditary syndromes such as Katrtagener's syndrome, cystic fibrosis, and some cases are idiopathic, having no known underlying cause.

Signs include adventitious breath sounds in virtually all patients, crepitations are present in 70%, wheezing in 34% and ronchi in 44%. In the past, digital clubbing was a frequent feature but a recent series describes a prevalence of only about 3%. Furthermore, fever, non-specific weight loss and anemia are frequently present among patients.

Treatment is focused on treating the underlying cause(s). Infections are usually treated empirically with antibiotics and recent studies have focused on aerosolized aminoglycosides which can reduce colonization by pseudomonas as in cystic fibrosis patients. Albuterol is the bronchodilator of choice and enhances mucociliary clearance. The benefits of chest physiotherapy, mucolytic agents, and postural drainage has not been established. Surgery is indicated for focal lesions with massive hemoptysis when conservative treatment fails. Angiographic embolization can be of use in selected cases.

Conclusion: Bronchiectasis is a disease with variable etiologies and clinical manifestations not truly typical of any one specific disease process. Despite our patient's wheeze, she did not improve with therapy for asthma. While her slight pedal edema improved with diuresis, her shortness of breath, cough and basilar crepitations did not improve until antibiotics were added following HRCT. Future treatments will be focused on primary prevention and localization of antibiotic delivery.

Neurosarcoidosis—A Diagnostic Difficulty. M.J. Bhutta (PGY 2), D. Modi and Intazam-u-Khan. Departments of Medicine and Neurology. Mount Sinai School of Medicine at Queens Hospital Center, Jamaica, NY.

Introduction: Neurosarcoidosis is an uncommon but serious, sometimes life-threatening manifestation of sarcoidosis. The diagnosis of neurosarcoidosis is often difficult, particularly in patients who lack either pulmonary or systemic manifestations. Neurologic sarcoid occurs in fewer than 10% of patients with sarcoidosis. We report a case with neurological manifestations as a sole presentation of sarcoidosis.

Case Report: A 44-year-old woman from Trinidad with no significant medical history presented to the emergency department complaining of lightheadedness, nausea, increasing difficulty walking and occasional vomiting for 3 days. Except for transient occasional double vision for 2–3 years, she denied fever, headache, recent viral illness, polyuria, polydipsia, tinnitis, hearing loss, ear pain, blurring of vision, vertigo, syncope or any menstrual irregularities. She also denied smoking, using alcohol or drugs and sexual promiscuity.

On examination she was not orthostatic. Neurologically she was alert and oriented. She had fluent speech with no anxious mood. Cranial nerve examination showed pupils 2–3 mm bilaterally equally reactive to light and accommodation. There was horizontal nystagmus with the fast phase towards the left side and good visual fixation. No other cranial nerve abnormalities were noted. The motor system was significant for spasticity in all four extremities, 3+ deep tendon reflexes and bilateral ankle clonus. Co-ordination showed intentional tremors, difficulty walking, spastic and ataxic gait, positive romberg's sign and difficulty in tendam walking. Finger to nose and heel to shin test were normal. There were no sensory abnormalities noted. Other systemic physical examination was essentially normal.

Initial laboratory studies including routine serum chemistries and liver function tests showed no significant abnormalities. Chest X-ray and a non-contrast CT scan of the head were within normal limits. Lumbar puncture revealed clear cerebrospinal fluid, normal opening pressure of 90 cm H2O, leukocytosis (WBC 23/cumm, normal: 0–5) and significant lymphocytosis 98% (40–80%). Low glucose 33 (40–80) and very high protein 214 (15–45) were noted in the cerebrospinal fluid. Neurology and infectious disease consults were requested. Serious consideration was given to tuberculous meningitis, CNS demyelinating disease, carcinomatous process, Lyme's disease, sarcoidosis, human T lymphotropic virus, human immunodeficiency virus or Herpes simplex virus infections. MRI with gadolinium showed diffuse leptomeningeal enhancement along the basilar, interpendicular and supra sellar cisterns and anterior to the pons and quadrigeminal spaces. Marked dural thickening of the cervicomedullary junction extending to the left cerebello-potine angle was also noted, strongly suggesting neurosarcoidosis. Tuberculous meningitis and eosinophilic granuloma could not be ruled out. The patient was treated with high-dose intravenous pulse methylprednisone. There was a dramatic clinical response over 2–3 days. CT of the chest was suspicious for sarcoidosis. A transbronchial biopsy from right upper lobe did not show sarcoidosis. A surgical consultant performed a biopsy of the right para tracheal lymph node via mediastinoscopy. The pathology report was non-caseating granuloma with negative stains for acid-fast bacilli and fungi. Other lab work-up showed normal levels of angiotensin-converting enzyme and vitamin D.

The patient was discharged after 2 weeks of clinical stability with steroid being tapered. She again presented to the emergency department two weeks later for a likely flare-up with similar but less intense manifestations, possibly secondary to the rapid steroid tapering. Her steroid dose was again increased with a good clinical response. The patient was discharged to be followed in the neurology clinic.

Discussion: Neurosarcoidosis is a rare disease with many presentations. It can appear in an acute, explosive fashion or as a slow, chronic illness. It can manifest as cranial neuropathy, aseptic meningitis, mass lesions, encephalopathy, vasculopathy, seizures, psychiatric manifestations, hydrocephalus, hypothalamic pituitary disorders, myelopathy, peripheral neuropathy or myopathy. Our case was unique in terms of signs and symptoms suggesting cerebellar area of involvement. MRI of the head was markedly abnormal with enhancement especially along cisternal and subarachnoid spaces without any evidence of a mass lesion.

Unlike pulmonary sarcoidosis where a period of observation is recommended for mild and asymptomatic cases, neurosarcoidosis should always be promptly treated. Treatment decisions are governed by disease location, clinical severity, time course and possible morbidity of the treatment. Corticosteroids are the cornerstone of therapy for neuro-sarcoidosis. Steroid therapy is usually started at a high dose and after a clinical response is achieved, the dose is gradually tapered. In patients where corticosteroids may be contraindicated, cytotoxic drugs such as methotrexate, azathioprine, cyclosporin, and cyclophosphamide have been used. Immunomodulators such as infliximab have been reported to be effective in a few cases with refractory sarcoidosis. Radiation therapy can also be used in patients who do not respond to drug therapy. Neurosurgical resection of intra cranial and spinal granulomas is only indicated in life-threatening situations or where medical treatment is insufficient.

A 46-Year-Old Man with Superior Pulmonary Sulcus Tumor and Pancoast Syndrome. O.I. Constantine and P. Rekha. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: Shoulder and arm pain from a superior sulcus tumor is a commonly misdiagnosed sign of lung cancer. The pain results from local extension of a tumor in the apex of the lung, with involvement of the eighth cervical and first thoracic nerves. Unfortunately, shoulder and arm pain are often mistaken for arthritis or bursitis of the shoulder, or cervical osteoarthritis.

Presentation of Case: A 46-year-old man with no medical history was referred to the medical clinic eleven weeks after his third emergency room visit because of right shoulder pain. The shoulder pain was worse with movement and was associated with mild numbness in the right hand. He also had a 4-month history of a burning sensation over the skin of the right shoulder and painful swelling of the right anterior chest wall. He denied fever, trauma, cough with sputum production, dyspnea, hoarseness, fever, chills, sweats, exposure to industrial dusts or carcinogens or weight loss. He had no surgical history and no allergies. He emigrated from Jamaica, West Indies and has a 20-pack-year history of tobacco use. He denied drug use and drank alcohol occasionally. He was unemployed.

His systems were negative for fever, night sweats, weight change, headache. He admitted to not sweating on the right side of the face in the last year. He denied shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, ankle swelling, dysphagia, nausea, vomiting, diarrhea, change in bowel movements or bone pains other than the right shoulder pain.

His vital signs were normal: BP 130/80 mmHg, pulse 80/min, respiration 12/min, temperature 98°F. On examination, the patient appeared well developed and well nourished. He had anicteric sclerae, pink conjunctivae and a moist buccal membrane. He had no palpable cervical, supraclavicular or axillary lymphadenopathy. There was no swelling and no tenderness of the shoulder joints but there was pain on performing movements at the right shoulder joint. He had no deformities and no paraspinal tenderness. The results of a neurologic examination were normal except for Horner's syndrome (ptosis, miosis, and anhydrosis) of the right eye. There was a tender, immobile, 2 × 2 centimetres upper right-sided diffuse swelling of the anterior chest wall. The lungs were clear to auscultation, his heart and abdominal examination revealed no abnormalities. He had no costovertebral angle tenderness. There was no peripheral edema or digital clubbing.

Microscopic examination of two CT scan-guided fine-needle aspiration biopsies of a 7 cm variegated mass involving the right apex revealed a poorly differentiated squamous cell carcinoma. CT scan of the brain without contrast was normal. Total body bone scan showed no evidence of skeletal metastasis. Echocardiography, renal and abdominal ultrasound studies were normal.

The diagnosis of a limited stage poorly differntiated non-small cell lung cancer stage 111B was made and the patient was treated with a course of concurrent radiation therapy and weekly Taxol and carboplastin. Over time, the patient showed clinical and radiologic evidence for local and metastatic relapse involving the brain and lumbar spine. He received external beam radiation to his brain with improvement. His lung cancer continued to progress and no further chemotherapy was recommended.

Discussion: Pancoast's description of the clinical and radiologic features, which led to the eponym, was published in 1924. The symptoms of the Pancoast syndrome include pain in the ipsilateral shoulder and arm along the distribution of the trunks of the eight cervical and first and second thoracic nerves, Horner's syndrome, and weakness and atrophy of the hand muscles. Phrenic nerve or recurrent laryngeal nerve involvement, the superior vena cava syndrome, and supraclavicular lymph node disease are less common.

Pancoast's syndrome may be the result of diverse neoplastic, inflammatory or infectious diseases or neurogenic thoracic outlet syndromes such as the cervical rib, and pulmonary amyloid nodules. It is, therefore, necessary to make a definitive diagnosis prior to treatment. The majority of patients with Pancoast's syndrome have non-small-cell brochogenic carcinoma, most commonly squamous, followed by adenocarcinoma, although in several series adenocarcinoma was the most frequent histologic type. Small-cell carcinoma is only rarely associated with this syndrome.

Relapse in the form of local or regional occurrence of disease or distant metastasis are common after the treatment of superior sulcus tumors. Brain metastasis is one of the most common forms of disease progression, especially with poorly differentiated large-cell carcinoma and adenocarcinoma. Hence, some authors recommend prophylactic cranial irradiation for these patients. Because of the peripheral location of the tumors that cause the Pancoast syndrome, patients rarely present with cough, hemoptysis, or dyspnea and hence are not diagnosed early. They are often initially treated for arthritis or bursitis of the shoulder, or cervical osteoarthritis. Pancoast tumor should be considered in the differential diagnosis of shoulder pain.

Nafcillin-Associated Hypokalemia—A Case Report. M. Gill, H. Gill, N. Gill, and I. Sachmechi. Department of Medicine, Mount Sinai School of Medicine, Queens Hospital Center, Jamaica, NY.

Introduction: A low-serum potassium concentration is one of the most common electrolyte abnormalities encountered in clinical practice. Even mild or moderate hypokalemia increases the risks of morbidity and mortality in patients with cardiovascular disease. As a result, when hypokalemia is identified, the underlying cause must be sought and the disorder treated. Antibiotics, which are the most commonly prescribed therapeutic agents in hospital, are one cause of hypokalemia that is often overlooked. We present a case of hypokalemia secondary to high dose nafcillin therapy.

Case Report: A 46-year-old normotensive, diet controlled diabetic African-American man presented to the emergency department with right flank pain of four days duration. Associated symptoms were dysuria, anorexia, weight loss, generalized weakness and back pain for about a month. On physical examination his vital signs were: blood pressure: 116/78 mm Hg, pulse rate: 88/min, respiratory rate: 18, temperature: 99.2°F. The rest of the physical examination was significant for a 6cms fluctuant non-tender submandibular swelling, left-sided pleural effusion and tenderness over the right costovertebral angle. The aspirated pleural fluid was consistent with empyema, and together with blood cultures, grew methicillin-sensitive *Staphylococcus aureus*. Transesophageal echocardiography did not reveal any valvular vegetations. There was evidence of osteomyelitis of the T12–L1 vertebrae. His submandibular swelling was drained of purulent material and his empyema required chest tube drainage. The patient was treated with intravenous nafcillin, followed by considerable clinical improvement. His hospital stay was complicated by severe and resistant hypokalemia, which remained uncorrected even with supplementation of up to 240 meq of potassium chloride every day. No non-renal cause to account for the hypokalemia was found, except that the patient had evidence of renal potasssium wasting with urine potassium of 37.6 meq/L. At this point, nafcillin was replaced with vancomycin, with gradual return of his potassium levels to normal over the next two weeks without necessitating potassium supplementation. It was concluded that nafcillin resulted in potassium wasting, which resolved after the drug was discontinued.

Discussion: Nafcillin is a very useful penicillinase-resistant antibiotic, commonly used in clinical practice. It also may have protean adverse drug manifestations such as high-dose nafcillin (>4 gm/day)-associated hypokalemia, by promoting renal potassium excretion due to increased sodium delivery to the distal nephron. This abnormality gradually reverses after the drug is discontinued or dosage is decreased.

Conclusion: The differential diagnosis of any patient with hypokalemia should include medications, especially drugs with high sodium content. This knowledge may save an otherwise extensive work-up for hypokalemia.

Life-Threatening Angioedema in SLE—A Case Report. H. Gill, M. Mutic, M. Gill, S. Kucinska, and A. Opran. Department of Medicine, Mount Sinai School of Medicine, Queens Hospital Center, Jamaica, NY.

Introduction: Systemic lupus erythematosus (SLE) can have protean manifestations involving virtually any organ system in the body. Life-threatening angioedema involving the upper respiratory tract is an unusual manifestation of SLE. We report a case of a 45-year-old Hispanic man who developed supraglottic edema causing airway obstruction requiring tracheostomy and mechanical ventilation, as well as treatment with high-dose IV steroids during the active disease process.

Case Report: A 45-year-old Hispanic man with history of SLE presented to the Emergency Department (ED) with one-day history of fever, sore throat, dysphagia and difficulty in breathing. He had pain and swelling of the knees and ankles for two months. He denied prior cough, sputum, pleuritic chest pain or similar illness, although he had been hospitalized several times for SLE flares. His vital signs in the ED were: blood pressure 153/94 mm Hg, temperature 97.1°F, pulse 88/min, respiratory rate 20/min, and O2-saturation of 98%. On examination, he had tongue swelling and inflammation of his knees and ankles. Otorhinolaryngologist was consulted and fibro optic nasopharyngeal laryngoscopy showed swelling of his tongue and uvula, supraglottic edema and airway obstruction. The patient was intubated and placed on mechanical ventilation. He also received high-dose intravenous steroids. Five days later, laryngoscopy showed complete resolution of supraglottic edema, biopsy of uvula and posterior pharynx was performed, and the tracheostomy was closed. Laboratory testing revealed a normal C1-inhibitor (C1-INH) level and increased lupus activity, evident by increased levels of CRP, anti-ds DNA, and decreased levels of C3 and C4. After an extra week in the rehabilitation department, the patient was discharged home.

Discussion: Angioedema is a condition characterized by the extravasation of fluid and its entry into interstitial tissues. It results from the release of inflammatory mediators that facilitate dilation end enhance the permeability of capillaries and venules. It is a rare occurrence in SLE and its mechanisms are heterogeneous. SLE can be associated with hereditary and acquired deficiencies of C1-INH or dysfunctional

C1-INH. Our patient did not have a personal or family history of angioedema and/or urticaria and his C1-Inhibitor level was within the normal range. He was not taking an ACE inhibitor or other medications known to have a potential to cause angioedema. He presented with a 2-day history of fever, odynophagia and sore throat and his lupus activity was increased as evidenced by arthritis of his knees and ankles, increasing levels of CRP and anti-dsDNA, and decreased levels of C3 and C4. Therefore, we suggest that it might have been an upper respiratory infection in the presence of active SLE that precipitated his angioedema.

Conclusion: Angioedema in SLE is a potentially fatal condition as the swelling of the tongue, uvula, soft palate, or larynx may compromise the airway. Timely securing of the airway and treatment of the underlying etiology ensure good outcomes.

Diltiazem as a Treatment for Soft Tissue Calcinosis in Adult Onset Dermatomyositis. G. Gupta, G. Mansouri, and A. Opran. Department of Internal Medicine, Mount Sinai School of Medicine, Queens Hospital Center, Jamaica, NY.

Introduction: Calcinosis, an accumulation of calcium hydroxyapatite, is often associated with dermatomyositis. Presentation of cutaneous calcinosis may range from hard painful nodular areas to stiffened areas in skin, cutaneous ulcer, joint contractures and muscle atrophy. Calcinosis associated with a connective tissue disorder is thought to be a localized process rather than a systemic disturbance in calcium homeostasis. A possible mechanism in dermatomyositis is release of mitochondrial calcium from cells into damaged muscle, which then forms a focus for dystrophic calcification. The calcinosis is very refractory in spite of treatment of the dermatomyositis, including the use of steroids and cytotoxic agents. Various calcium channel blockers have been tried to treat calcinosis but only diltiazem has been shown to be effective for calcinosis in juvenile onset dermatomyositis. We report a case of adult onset dermatomyositis with calcinosis, treated with diltiazem, who had a significant clinical improvement of the calcinosis.

Case Report: A 55-year-old woman with active dermatomyositis presented with a 3-week history of generalized weakness and myalgia of limbs, muscle stiffness and worsening of rashes around the periorbital areas. Physical examination was positive for fever. Diffuse flat erythema in a shawl-like distribution was observed over the thorax and shoulders, in a V-shaped distribution over the anterior neck and chest, over the forehead, malar region and chin with a heliotrope rash on the upper eyelids accompanied by swelling of the eyelid. A violaceous erythematous rash was present over the extensor surfaces of the patient's metacarpophalangeal and interphalangeal joints of the fingers. She also had multiple tender, hard nodular lesions on both anterolateral areas of the thigh, right arm and sacral areas.

Laboratory findings were consistent with active dermatomyositis with a serum ANA titer of 1:1280, the creatinine kinase was increased to 1194 units/L. Radiographic analysis of pelvic and leg areas showed subcutaneous ossification/calcification in the soft tissue of the thigh. Bone densitometry showed increased bone mineral density in the femoral areas. The patient was receiving prednisone 10 mg orally once a day before hospitalization. This medication was changed to methylsuccinate prednisone 60 mg via intravenous route during the hospitalization. High-dose steroid therapy together with methotrexate and hydroxychloroquine treatment resulted in significant improvement in symptoms except around the calcific nodular areas, which were still painful. The patient was started on diltiazem for calcinosis, which resulted in significant improvement in pain around the areas of calcinosis and clinical improvement of the skin lesions.

Conclusion: Previous drugs used to treat ectopic calcification have included bisphosphonates, probenecid, aluminium hydroxide, warfarin and the local injections of glucocorticoids. Unfortunately, none have shown more than anecdotal success. The finding in our patient that long-term treatment with diltiazem resulted in significant improvement in calcinosis suggests that diltiazem, an L-type calcium channel blocker may offer more consistent therapeutic benefit.

Case Report: Adult Intussusception. Y. Hiltzik MS IV (NYCOM), R.A. Paguia, F. Wibowo, L. Kasturi, and A. Moskowitz. Department of Medicine, Mount Sinai School of Medicine/Queens Hospital Center, Jamaica, NY.

Intussusception is the invagination of a segment of bowel into the lumen of an immediately adjacent segment of bowel. The intussusceptum is the proximal segment of the bowel that prolapses into the distal adjacent segment, which is called the intussuscipiens. Intussusception occurs most commonly in children, accounting for most cases of intestinal obstruction. In adults, however, it is very rare, but when present, a cause is frequently identified in up to 90% of cases.

We report the case of a 48-year-old woman who presented with a 2-week history of intermittent, colicky, epigastric pain with accompanying nausea associated with oral intake but no vomiting. Symptoms resolved spontaneously. No bleeding per rectum or change in bowel habits or caliber of stool was reported. Last bowel movement was 4 days prior to hospitalization. The patient's medical history includes diabetes, hypertension, hyperlipidemia and esophageal reflux. The patient had 2 prior caesarean sections. There was no history of alcohol, tobacco or drug use. Home medications consist of insulin, pioglitazone, metformin, hydrochlorothiazide, gabapentin (for neuropathy secondary to diabetes) and fosinopril. Family medical history was notable for hypertension and diabetes. On examination, the patient appeared comfortable, with a blood pressure of 186/68 mm Hg, pulse rate of 100 beats per minute and respiratory rate of 12 breaths per minute. Patient was afebrile. Lungs were clear and there were no murmurs or extra heart sounds on auscultation. The patient was noted to have an obese soft abdomen but with direct tenderness over the epigastric and right upper quadrant areas, with no rebound or guarding; no masses or organomegaly were felt. Digital rectal exam showed external hemorrhoids, normal tone, no masses and heme negative stools. Apart from slight anemia, the patient's routine laboratory studies were unremarkable. Chest X-ray revealed only minimal cardiomegaly. Abdominopelvic CT scan showed colo-colonic intussusception at the level of the transverse colon. Colonoscopy done to evaluate the intussusception revealed an ulcerated villous adenoma tethered to the bowel wall at the mid transverse colon region. The patient subsequently underwent right hemicolectomy with no complications. Postoperative course was uneventful, and the patient went home on postoperative day five.

Intussusception in adults is a rare phenomenon; 85–90% of intussusception occurs during childhood, where it is the leading cause of bowel obstruction. The cause is not established, although it is believed that hypertrophy of Peyer's patches in the terminal ileum acts as the pathologic lead point in causing the invagination of the bowel segments. By contrast, adult intussusception has an identifiable cause in 90% of cases, mostly a neoplasm in the colon rather than in the small bowel. Other causes include postoperative adhesions, diverticuli, sprue, and HIV disease. The clinical presentation can be variable; often patients present with a chronic intermittent pain pattern that suggests chronic subacute intermittent partial bowel obstruction. Surgical resection is the definitive treatment in most cases due to the high incidence of malignancy.

Severe Progressive Halothane Hepatitis with Remarkable Resolution after Treatment with Steroids. S. Parab, S. Siripurapu, M. Shulimovich MS III (NYCOM), and E. Restrepo. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: Halothane is an inhalational anesthetic, commonly used worldwide, which may cause idiosyncratic reactions in adults, leading to hepatotoxicity. The resulting liver injury may vary in severity from a mild hepatitis without complications to severe fulminant hepatitis with hepatic failure leading to death. This type of liver damage has clinical, serological and immunological features compatible with an immune-mediated reaction. The treatment of halothane hepatitis is mainly supportive. The use of corticosteroids in this setting remains controversial, given the lack of controlled studies in the literature to support its use.

This case report describes a patient who developed symptomatic hepatitis following exposure to halothane, with progressive gradual clinical deterioration. The patient showed a rapid and sustained improvement following initiation of therapy with prednisone.

Case Report: A 58-year-old woman from Guatemala with a medical history of gastroesophageal reflux disease (GERD) and chronic sinusitis presented to the emergency department with complaints of fever with chills, generalized body ache and weakness for two days, and nausea, vomiting and diarrhea for one day. Ten days earlier, she had undergone sinus surgery (recannulation) under general anesthesia in Guatemala without any complications. After surgery she was prescribed a non-steroidal anti-inflammatory (NSAID) as well as a quinolone antibiotic for seven days. She was doing well when she travelled to New York 5 days after surgery. On the 6th day, she developed the above-mentioned symptoms. The patient was taking only acetaminophen 650 mg every four hours for two days prior to admission, to ease her pain and fever.

In the ER, her blood pressure was 80/40 mm Hg, pulse 117 bpm, respiratory rate 20 breaths per minute and temperature 100.8° F. Physical examination was significant for slight jaundice, right upper quadrant abdominal tenderness, and some maxillary tenderness.

The initial laboratory tests revealed a serum aspartate transaminase (AST) of 1159 units/L, serum alanine transaminase (ALT) of 1,049 units/L, total bilirubin 3.5 mg/dL, alkaline phospahatase 152 units/L. The white blood cell count was 13,600/mL with 70% neutrophils, 14% bands and 4% eosinophils. The prothrombin time was prolonged, at 19.8 seconds (INR2.58), and partial thromboplastin time was 36.1 seconds. Chest X-ray revealed no abnormalities. Abdominal ultrasound was unremarkable except for a small cyst in the upper pole of the right kidney. Hepatitis A, B and C serologies as well as leptospira antibodies were negative. Acetaminophen level was less than 10 mcg/mL and serum ANA titer was negative.

By the tenth hospital day, anorexia, nausea and vomiting persisted, and the patient was markedly jaundiced and experienced periods of mild confusion despite treatment with lactulose. On repeat blood tests, the AST peaked at 2,256 units/L, ALT at 1,176 units/L, total bilirubin rose to 23.1 mg/dL and eosiniphilia increased to 17% (absolute eosinophil count 1,768/ mL). CT of the abdomen showed common bile duct dilatation and a questionable duct stone. Subsequently the patient underwent an unsuccessful endoscopic retrograde cholagio pacreatography (ERCP), followed by magnetic resonance cholagio pacreatography (MRCP), which confirmed the dilation of the common bile duct.

Additional information was obtained from Guatemala. The patient had received the anesthetic halothane during her recent sinus surgery. At this point, the diagnosis of halothane-induced hepatotoxicity was strongly considered. In view of the patient's progressive clinical deterioration while receiving supportive treatment, and the unpredictable course of halothane-induced hepatitis the patient was given a trial of corticosteroids. Treatment with a tapering course of prednisone starting with 60 mg daily was given over the course of two weeks. On the 3rd day of prednisone therapy the patient reported feeling significantly better with complete resolution of nausea and vomiting, and improved appetite. The liver function tests also showed marked improvement and the jaundice promptly cleared. Follow-up abdominal ultrasound performed 12 days after starting prednisone revealed resolution of the common bile duct dilatation. Four months after hospital discharge the patient reported feeling well.

Discussion: The clinical diagnosis of halothane-induced hepatitis was made in this patient. Ten days after receiving halothane anesthesia, she developed the characteristic clinical picture of fever, anorexia, nausea, myalgias, jaundice, marked elevation of serum transaminases and eosinophilia. In addition, there was no evidence for viral, autoimmune or metabolic causes of hepatitis. Halothane hepatitis is due to hepatocellular damage caused by an immune response directed against hepatocytes with trifluoroacetate (TFA) protein adducts. TFA (trifluoroacetate) is a metabolite of halothane, which binds to hepatocyte macromolecules and phospholipids producing TFA-protein adducts which act as sensitizing neoantigens leading to fulminant hepatic necrosis.

Although the general consensus in the management of halothane hepatitis is supportive therapy, the fact that halothane-induced hepatotoxicity constitutes an immune-mediated idiosyncratic reaction with an unpredictable course including fulminant hepatitis and even death, a trial with prednisone should be considered in patients who have evidence of severe halothane-induced liver injury such as the case presented here. Therapy with prednisone appears to decrease morbidity and hasten the resolution of the immune process. In the U.S., halothane has not been used in adults since 1970s. However, it continues to be used commonly in other countries and should be considered in the differential diagnosis in an immigrant patient presenting with liver dysfunction in the postoperative period.

A Walk in the Desert: Corticosteroids in Disseminated Coccidioidomycosis. N. Popovic, R. López. Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

LR was a 28-year-old Spanish-speaking man from Guatemala who entered the U.S. five months prior to presentation by walking from Mexico across the Arizona desert three times. He complained of loss of appetite and a 50 lb weight loss over 2 months, cough productive of whitish sputum, loose stool without mucus or blood, and subjective fever for one month. He denied using drugs, smoking cigarettes, or using alcohol; he also denied risk factors for HIV or TB exposure. The patient had no previous medical problems and did not take medications.

On examination the patient was cachectic, blood pressure was 102/62 mmHg, heart rate was 142 bpm and he had a fever of 103° F. Respiratory rate was 20. He had coarse breath sounds with crackles more prominent in the left lung field. His inguinal lymph nodes were enlarged without induration. The remainder of his physical examination was normal. Laboratory data revealed a normocytic anemia with a normal white blood cell and differential counts; serum chemistries revealed sodium 124, potassium 2.5, chloride 91, glucose 146 and calcium 7.5. His chest X-ray revealed patchy bilateral infiltrates.

The patient was hospitalized and treated for community-acquired pneumonia. He continued to have daily fevers (T_{max} 104.2° F), and his bowel movements remained loose. Anemia work-up was consistent with the anemia of chronic disease. CT of his chest revealed extensive parenchymal consolidation in the upper lobes associated with numerous acinar nodules and extensive mediastinal and left hilar adenopathy as well as bilateral pleural effusions. A CD4 count was 51 cu/mm, CD4/CD8=0.08. Empiric therapy for *Pneumocystis carinii* pneumonia and TB were added to his treatment. The patient was transferred to the ICU because of hypotension (BP was 80/54 mm Hg) that responded to aggressive fluid replacement. A bone marrow aspiration and biopsy was non-diagnostic. Bronchoalveolar lavage revealed negative smears for *P. carinii*, acid-fast bacilli and fungus. Transbronchial biopsy revealed unremarkable lung with no granuloma. Ophthalmology consultation revealed small, flat, white lesions, which were felt to be nonspecific findings. The patient was intubated and started on pressor drugs for hypotension (BP was 70/50 mmHg) and tachypnea. A random cortisol level was 9.93 Ug/dL; hydrocortisone was given for presumed adrenal insufficiency. Blood cultures were reported to show gram positive cocci in clusters and vancomycin and empiric amphotericin B was added to this treatment regimen. The patient steadily deteriorated and met the criteria for acute respiratory distress syndrome; he later developed a tension pneumothorax which was emergently decompressed with angiocatheter. Right 18 French Chest tube was placed in the right lung.

The blood cultures previously reported to contain gram positive cocci in clusters were corrected and were than reported to be growing mold. No changes were made in management. The patient expired shortly thereafter.

Postmortem laboratory coccidioidomycosis results included all blood cultures growing fungus. Bronchoalveolar lavage and transbronchial biopsy cultures were negative for acid-fast bacilli. Transbronchial biopsy grew *Coccidioides immitis*. His bone marrow biopsy was negative for fungus.

Conclusion: The definitive diagnosis may be made too late to save the patient, as there is no reliable rapid testing method to diagnose this condition. Despite the fact that *C. immitis* is capable of growing in bacterial blood culture media, it is a lengthy process and can be mistaken for gram positive bacteria as occurred in our case. However, diffuse pneumonia with a reticulonodular pattern in a patient with an appropriate travel history should serve as a clue to raise the index of suspicion to consider coccidioidomycosis as a diagnosis.

Most Coccidioides infections do not require treatment, and those that do usually respond to antifungal therapy. Fulminant coccidioidomycosis is a more serious condition; a recent report of a case of fulminant coccidioidomycosis in an immunocompetent patient with severe acute respiratory distress syndrome stated that the use of corticosteroids in addition to standard antifungal treatment produced a good outcome. However, this observation does not seem to apply in our case and others. Contrary to the well-established use of corticosteroids in the treatment of PCP pneumonia and sepsis, use of corticosteroids in coccidioidomycosis is controversial. A retrospective study of immunocompromised patients with hematologic malignancy did not support the use of corticosteroids in the management of disseminated coccidioidomycosis.

Until 2004 only 11 cases of septic shock due to coccidioidomycosis were described without long-term survival. In November 2004 the first successful outcomes in patients with septic shock due to coccidioidomycosis were reported in immune competent patients. Two cases of septic shock associated with coccidioidomycosis that were successfully treated with *drotrecogin alfa* (activated) in combination with antifungal agents.

This reported case highlights the need for further investigation of the role of corticosteroids in respiratory failure due to coccidiodomycosis. It also highlights the impact that world travel imposes on physicians all over the world, who need to be ready to diagnose problems limited to small endemic areas in addition to the interrelations these problems may have with a growing population of immunocompromised patients.

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Dean's Lecture

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CYP2E1—Biochemical and Toxicological Aspects and Role in Alcohol-Induced Liver Injury

ARTHUR I. CEDERBAUM, PH.D.

Abstract

Ethanol-induced oxidative stress appears to play a major role in mechanisms by which ethanol causes liver injury. Many pathways have been suggested to contribute to the ability of ethanol to induce a state of oxidative stress. One central pathway appears to be the induction of the CYP2E1 form of cytochrome P450 enzymes by ethanol. CYP2E1 is of interest because of its ability to metabolize and activate many toxicological substrates, including ethanol, to more reactive toxic products. Levels of CYP2E1 are elevated under a variety of physiological and pathophysiological conditions, and after acute and chronic alcohol treatment. CYP2E1 is also an effective generator of reactive oxygen species such as the superoxide anion radical and hydrogen peroxide, and in the presence of iron catalysts, it produces powerful oxidants such as the hydroxyl radical. This review article summarizes some of the biochemical and toxicological properties of CYP2E1, and briefly describes the use of HepG2 cell lines developed to constitutively express the human CYP2E1 in assessing the actions of CYP2E1. Regulation of CYP2E1 is quite complex and will be briefly reviewed. Future directions in research, which may help clarify the actions of CYP2E1 and its role in alcoholic liver injury, are suggested.

Keys Words: CYP2E1, alcohol, oxidative stress, liver injury, reactive oxygen species, proteasome, hepG2 cells.

Introduction

Cytochrome P450 and Oxidative Stress

THE CYTOCHROME P450 ENZYMES are a superfamily of hemeproteins that serve as terminal oxidases in the mixed function oxidase system for metabolizing various endogenous substrates such as steroids and fatty acids, and xenobiotics including drugs, toxins and carcinogens (1). Many different enzymes belong to this P450 family; P450s are present in virtually all living organisms. A systematic nomenclature was developed for the P450 family; it is based on the sequence identity of the different P450s (2). The enzymes are named CYP for cytochrome P450, followed by an Arabic number denoting the family (more than 40% identity on the amino acid sequence level), a letter designating the subfamily (more than 55% identity) and, finally, an Arabic numeral representing the individual gene in the subfamily. The P450s catalyze many different chemical reactions, including monooxygenation, peroxidation, reduction, dealkylation, epoxidation, and dehalogenation (3, 4). Many structurally diverse compounds can be metabolized by P450 enzymes. A major function of P450-catalyzed reactions is to convert a compound into a more polar metabolite that can be easily excreted by the organism directly or in a conjugated form by the action of phase II enzymes. With some compounds, e.g., carbon tetrachloride or acetaminophen, metabolism by P450 can give rise to toxic metabolites that damage cells. For P450s to function catalytically, flavoprotein reductases such as NADPH-cytochrome P450 reductase, adrenodoxin and adrenodoxin reductase, are necessary to transfer electrons from reduced nicotinamide adenine dinucleotide phosphate (NADPH) or reduced nicotinamide adenine dinucleotide (NADH) to reduce the heme group from the ferric redox state to the ferrous state. The latter step is necessary to bind molecular oxygen to form the oxygenated P450

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Glossary

AA = arachidonic acid
ALD = alcoholic liver disease
AMP = adenosine monophosphate
ATP = adenosine triphosphate
BSO = L-buthionine sulfoximine
CYP = cytochrome P450
DAS = diallyl sulfide
GCLC = catalytic subunit of glutamate-cysteine ligase
GCLM = modulatory subunit of glutamate-cysteine ligase
GSH = glutathione
HNE = 4-hydroxynonenal
H_2O_2 = hydrogen peroxide
HSC = hepatic stellate cells
Km = enzymatic kinetic constant
LOOH = lipid hydroperoxide
MDA = malondialdehyde
MEOS = microsomal ethanol oxidizing system
NAD^+ = nicotinamide adenine dinucleotide
NADH = nicotinamide adenine dinucleotide, reduced
NADPH = nicotinamide adenine dinucleotide phosphate, reduced
NASH = non-alcoholic steatohepatitis
$O_2^{\bullet -}$ = superoxide anion radical
PNP = 2,4-para-nitrophenol
PSI = Czb-I1e-Glu (OtBu)-Ala-Leucinal
ROS = reactive oxygen species
UV = ultraviolet
$\Delta\psi_m$ = mitochondrial membrane potential

complex that catalyzes the diverse chemical reactions mentioned above (5).

Oxygen activation by P450, necessary for the enzyme catalytic function, can also result in the production of reactive oxygen species (ROS). Small amounts of the superoxide anion radical ($O_2^{\bullet -}$) can be produced from decay of the oxygenated P450 complex, while hydrogen peroxide (H_2O_2) can form from either dismutation of $O_2^{\bullet -}$ or decay of the peroxy P450 complex (6, 7). ROS have been implicated in many of the major conditions: ischemia-reperfusion injury; cardiovascular diseases; atherosclerosis; carcinogenesis; diabetes; neurodegenerative disorders (e.g., Parkinson's and Alzheimer's diseases); toxicity of heavy metals (e.g., iron); asbestos injury; radiation injury; vitamin deficiency; drug (e.g., redox recycling agents) toxicity; inflammation; smoke toxicity; emphysema; and toxicity associated with acute and chronic ethanol ingestion (8 – 10), as well as the aging process.

ROS can be produced from many systems in cells, including the mitochondrial respiratory chain, the cytochrome P450s, oxidative enzymes such as xanthine oxidase, aldehyde oxidase, cyclooxygenase, monoamine oxidase, and the NADPH oxidase complex, from auto-oxidation of heme proteins such as ferrohemoglobin or myoglobin, or from biochemicals such as catecholamines, quinones or tetrahydrobiopterins. Environmental sources include ultraviolet (UV) radiation, smoke and certain drugs which are metabolized to radical intermediates or which can cause redox cycling. ROS are toxic to cells because they can react with most cellular macromolecules, inactivating enzymes, causing DNA damage and peroxidation of lipids, which can result in destruction of biological membranes. A variety of enzymatic and non-enzymatic mechanisms have evolved to protect cells against ROS, including the superoxide dismutases which remove $O_2^{\bullet -}$; catalase and the glutathione (GSH) peroxidase system which remove H_2O_2; glutathione *S*-transferases which can remove reactive intermediates and lipid aldehydes; metallothioneins, heme oxygenases, thioredoxins; ceruloplasmin and ferritin which help remove metals such as iron, which promotes oxidative reactions; non-enzymatic, low molecular weight antioxidants such as GSH, vitamins A, C and E, ubiquinone, uric acid, bilirubin (11, 12). Oxidative stress, i.e., toxicity by ROS, reflects a balance between the rate of production of ROS and the rates of removal of ROS plus repair of damaged cellular macromolecules. While excess ROS can cause toxicity, macrophages and neutrophils contain an NADPH oxidase that produces ROS, which destroy foreign organisms (13), and the enzyme myeloperoxidase catalyzes a reaction between H_2O_2 and chloride to produce the powerful oxidant hypochlorite, which helps destroy foreign invaders. In addition, ROS at low concentrations, especially H_2O_2, may be important in signal transduction mechanisms in cells (14).

Alcohol, Oxidative Stress and Cell Injury

The ability of acute and chronic ethanol ingestion to increase production of reactive oxygen species and enhance peroxidation of lipids, protein, and DNA has been demonstrated in a variety of systems, cells, and species, including humans. Much has been learned about alcohol metabolism, the various enzymes and pathways involved, and how alcohol, directly via its metabolism, or indirectly via its solvent-like action affecting cellular membranes, impacts on cell function. Yet despite this tremendous growth in understanding of alcohol metabolism and actions, the mechanism(s) by which alcohol causes cell injury are still not clear. A variety of leading mechanisms have been briefly summarized (10, 15, 16), and it is likely that many of them ultimately converge as they reflect a spectrum of the organism's response to the myriad of direct and indirect actions of alcohol. A major mechanism that is a focus of considerable research is the role of lipid peroxidation and oxidative stress in alcohol toxicity.

Many pathways have been suggested to play a key role in how ethanol induces "oxidative stress." Some of these include redox state changes (decrease in the nicotinamide adenine dinucleotide [NAD+]/NADH redox ratio) produced as a result of ethanol oxidation by alcohol and aldehyde dehydrogenases; production of the reactive product acetaldehyde as a consequence of ethanol oxidation by all major oxidative pathways; damage to mitochondria, which results in decreased adenosine triphosphate (ATP) production; direct or membrane effects caused by hydrophobic ethanol interaction with either phospholipids or protein components or enzymes; ethanol-induced hypoxia, especially in the pericentral zone of the liver acinus as oxygen is consumed in order for the liver to detoxify ethanol via oxidation; ethanol effects on the immune system, and altered cytokine production; ethanol-induced increase in bacterial-derived endotoxin with subsequent activation of Kupffer cells; ethanol induction of CYP2E1; ethanol mobilization of iron, which results in enhanced levels of low molecular weight non-heme iron; effects on antioxidant enzymes and chemicals, particularly mitochondrial and cytosolic glutathione; one electron oxidation of ethanol to the 1-hydroxy ethyl radical; conversion of xanthine dehydrogenase to the xanthine oxidase form. Again, many of these pathways are not exclusive of one another, and it is likely that several, indeed many, systems contribute to the ability of ethanol to induce a state of oxidative stress.

What is the evidence that ethanol-induced oxidative stress plays a role in cell injury? While many studies have shown increases in lipid peroxidation or protein carbonyl formation by alcohol, it is not always clear if these are causes or consequences of the alcohol-induced tissue injury. Nevertheless, there are many studies that show that administration of antioxidants or iron chelators or GSH-replenishing agents can prevent or ameliorate the toxic actions of alcohol. The most convincing data that oxidative stress contributes to alcohol-induced liver injury comes from the studies using the intragastric infusion model of alcohol administration. In these studies, alcohol-induced liver injury was associated with enhanced lipid peroxidation, protein carbonyl formation, formation of the 1-hydroxyethyl radical, formation of lipid radicals, and decreases in hepatic antioxidant defense, especially GSH (17–22). Replacement of polyunsaturated fat (required for lipid peroxidation to occur) with saturated fat or medium chain triglycerides in the diets fed to rats intragastrically, lowered or prevented the lipid peroxidation, and the alcohol-induced liver injury. Thus, alcohol plus polyunsaturated fat was required for the injury to occur. Addition of iron, known to generate $^{\bullet}OH$ and promote oxidative stress, to these diets exacerbated the liver injury (20). Significantly, addition of antioxidants such as vitamin E, ebselen, superoxide dismutase, and GSH precursors prevented the alcohol-induced liver injury (17, 23, 24).

In addition to these *in-vivo* studies, *in-vitro* studies with hepatocytes also showed that ethanol can produce oxidative stress and hepatocyte toxicity. Studies with isolated hepatocytes from control rats or chronically ethanol-fed rats indicated that ethanol metabolism via alcohol dehydrogenase results in an increase in ROS production, hepatocyte injury, and apoptosis, reactions blocked by antioxidants (25, 26). Studies in our laboratory with HepG2 cell lines expressing CYP2E1 showed that addition of ethanol or polyunsaturated fatty acids or iron, or depletion of GSH, resulted in cell toxicity, increased oxidative stress and mitochondrial damage, reactions prevented by antioxidants (27). Since CYP2E1 plays a role in ethanol-induced oxidant stress and is a minor pathway of ethanol oxidation, the biochemical and toxicological properties of CYP2E1 will form the basis for the remainder of this review.

Biochemistry and Toxicology of CYP2E1

CYP2E1 and the Microsomal Ethanol Oxidizing System

Alcohol dehydrogenase is the major enzyme pathway for oxidizing ethanol to acetaldehyde. A microsomal ethanol oxidizing system (MEOS) was characterized by Lieber and associates and shown to be dependent on P450 (28). The Km for ethanol oxidation by the MEOS (about 10 mM) was about an order of magnitude greater than that for ethanol oxidation by alcohol dehydrogenase. Acetaldehyde is the reactive product resulting from ethanol oxidation; MEOS represents a minor pathway of ethanol oxidation, probably accounting for less than 10% of the liver capacity to oxidize ethanol (29). Significantly, activity of MEOS is enhanced after chronic ethanol exposure, partly due to an increased total content of P450, in particular the induction of CYP2E1, a member of the P450 family showing high catalytic activity for ethanol (28, 29). Induction of MEOS may play an important role in the metabolic tolerance found after chronic ethanol consumption, i.e., an increased capacity to oxidize ethanol. While there was early controversy over the nature of MEOS, the purification of an ethanol-inducible form of P450 from rabbit liver microsomes firmly established the role of P450 in MEOS (30). Ethanol-inducible P450s have been isolated from many species; while several P450s may be induced by ethanol, the major inducible P450 is now referred to as CYP2E1.

CYP2E1 Localization

CYP2E1 is mainly found in the liver, although significant amounts are found in most organs. Within the liver acinus, the levels of CYP2E1 are highest in the centrilobular zone (31). This is of interest because toxins such as ethanol, acetaminophen, nitrosamines, and carbon tetrachloride, which are substrates of CYP2E1, preferentially destroy the centrilobular liver region. In liver, CYP2E1 is expressed mainly in the hepatocytes, but significant amounts are also found in the Kupffer cells; both hepatocyte and Kupffer cell CYP2E1s are inducible, e.g., by ethanol. CYP2E1, like other xenobiotic-metabolizing P450s, is mainly located in the membrane of the endoplasmic reticulum, where it is anchored and retained through its hydrophobic NH_2-terminus, leaving the large COOH-terminal domain, including the catalytic site, exposed to the cytosol. CYP2E1 has also been detected in other cellular compartments such as the plasma membrane (32), where it may play a role in the autoimmune hepatotoxicity observed in patients suffering from alcoholic liver disease (ALD) (33). CYP2E1 was shown to be transported out of the endoplasmic reticulum to the Golgi apparatus, with subsequent transfer to the plasma membrane (34). Removal or modification of the hydrophobic NH_2-terminal transmembrane domain of CYP2E1 results in the exposure of a mitochondrial-targeting signal that directs the protein to the mitochondria. The mitochondrial targeting signal of rat liver CYP2E1 was identified and demonstrated to be located between amino acid residues 74 and 95, an area rich in positively charged amino acids and also containing a hydrophobic region (35). A phosphorylated form of mitochondrial CYP2E1 was also observed with a molecular weight of 54 kDa; this form could be induced by pyrazole treatment (36).

CYP2E1 Substrates

Perhaps the most important endogenous substrate of CYP2E1 is acetone, which is converted to acetol and methylglyoxal; the three are carbon intermediates that can ultimately produce glucose (37). Blood levels of acetone under fasting conditions were elevated up to 50-fold in transgenic mice lacking CYP2E1 as compared to wild type mice, indicating the critical role of CYP2E1 in acetone metabolism (38). Other endogenous compounds that can be metabolized by CYP2E1 include fatty acids such as linoleic and arachidonic (AA) acids (39). With respect to exogenous substrates, CYP2E1 metabolizes a variety of small, hydrophobic substrates including solvents such as chloroform and carbon tetrachloride, aromatic hydrocarbons such as benzene and toluene, alcohols such as ethanol and pentanol, aldehydes such as acetaldehyde, halogenated anesthetics such as enflurane and halothane, nitrosamines such as *N,N*-dimethylnitrosamine, and drugs such as chlorzoxazone and acetaminophen. The table, adapted from Koop, 1992 (40); Lieber, 1997 (28); Raucy et al., 1993 (41); Tanaka et al., 2000 (42); and Bolt et al., 2003 (43), lists some of the substrates which are effectively metabolized by CYP2E1. From a toxicological point of view, interest in CYP2E1 revolves around the ability of this P450 enzyme to metabolize and activate many toxicologically important compounds such as ethanol, carbon tetrachloride, acetaminophen, benzene, halothane and many other halogenated substrates. Procarcinogens, including nitrosamines and azo compounds, are effective substrates for CYP2E1 (44). Toxicity by the above compounds is enhanced after induction of CYP2E1, e.g., by ethanol treatment, and toxicity is reduced by inhibitors of CYP2E1. Of the substrates mentioned in Table 1, chlorzoxazone is of special value, as its hydroxylated product can readily be assayed in the blood, and the 6-hydroxychlorzoxazone/chlorzoxazone ratio is widely used to assess the approximate levels of CYP2E1 in humans, including alcoholics (45).

Molecular oxygen is a most important substrate for CYP2E1. Relative to several other P450 enzymes, CYP2E1 displays high NADPH oxidase activity, as it appears to be poorly coupled with NADPH-cytochrome P450 reductase (46, 47). CYP2E1 was the most efficient P450 enzyme in the initiation of NADPH-dependent lipid peroxidation in reconstituted membranes among five different P450 forms investigated. Furthermore, anti-CYP2E1 IgG inhibited microsomal oxidase activity and lipid peroxidation dependent on P450 (47). We found that microsomes isolated from rats fed

TABLE

Substrates Metabolized/Activated by CYP2E1 (40–43).

Alcohols, aldehydes, ketones	Aromatic compounds	Ethers	Fatty acids	Halogenated and non-halogenated alkanes and alkenes	Nitrosamines, azocompounds	Reducible substrates
Acetaldehyde	Acetaminophen	Diethyl ether	Arachidonic acid (ω-1 and ω-2 hydroxylation)	Acetoacetate	Azoxymethane	*t*-Butylhydroxyperoxide
Butanol	Aniline	Methyl *t*-butyl ether		Acetol	*N*,*N*-Diethylnitrosamine	Carbon tetrachloride
2-Butanone	Benzene		Lauric acid (ω-1 hydroxylation)	Acetone	*N*,*N*-Dimethylnitrosamine	Chromium [Cr(VI)]
Ethanol	Bromobenzene			Acetonitrile (+ catalase)	Methylazoxymethanol	Oxygen
Glycerol	Caffeine			Acrylonitrile	*N*-Nitroso-2,3-dimethylmorpholine	
Isopropanol	Capsaicin			1,3-Butadiene	*N*-Nitrosopyrrolidine	
Methanol	Chlorzoxazone			Chloroform		
Pentanol	3-Hydroxypyridine			Chloromethane		
Propanol	Isoniazid			Dibromoethane		
	Phenol			Dichloromethane		
	p-Nitrophenol			1,1-Dichloroethane		
	Pyrazole			1,1-Dichloroethylene		
	Pyridine			1,2-Dichloropropane		
	Styrene			*N*,*N*-Dimethylacetamide		
	Tamoxifen			*N*,*N*-Dimethylformamide		
	Toluene			Enflurane		
				Ethane		
				Ethyl carbamate		
				Ethylene dichloride		
				Halothane		
				Hexane		
				Methylene chloride		
				N-Methylformamide		
				Pentane		
				Thioacetamide		
				Trichloroethylene		
				Vinyl bromide		
				Vinyl chloride		

ethanol chronically were about 2- to 3-fold more reactive in generating $O_2^{\bullet -}$ and H_2O_2 and, in the presence of ferric complexes, in generating $^{\bullet}OH$ and undergoing lipid peroxidation (48, 49). CYP2E1 levels were elevated about 3- to 5-fold in liver microsomes after feeding rats the Lieber-DeCarli diet for 4 weeks. Microsomes isolated from the ethanol-fed rats were more reactive in catalyzing DNA strand cleavage when plasmid DNA was added to the microsomal incubation system (49). The enhanced effectiveness of liver microsomes isolated from the ethanol-fed rats was prevented by addition of chemical inhibitors of CYP2E1 and by polyclonal antibody raised against CYP2E1, confirming that the increased activity in these microsomes was due to CYP2E1.

CYP2E1 is a minor pathway of ethanol oxidation, as it catalyzes the two-electron-oxidation of ethanol to acetaldehyde. Interestingly, acetaldehyde is also a substrate for CYP2E1 and is oxidized to acetate; thus, CYP2E1 can, at least theoretically, catalyze the oxidation of ethanol to acetate. However, this oxidation is likely to be negligible in the presence of ethanol, the substrate that generates acetaldehyde (50). CYP2E1 can also promote the one-electron oxidation of ethanol to the 1-hydroxyethyl radical (51). The mechanism for this oxidation is not clear but appears to involve the oxidase activity of CYP2E1 rather than a direct metabolism by CYP2E1, since production of the 1-hydroxyethyl radical is inhibited by ROS scavengers such as superoxide dismutase and catalase (52, 53). Detection of the 1-hydroxyethyl radical in the bile after administration of ethanol to rodents has been a most valuable assay for determining ethanol-induced radical formation and oxidant stress *in vivo* (54). Formation of the 1-hydroxyethyl radical may play a role in the development of liver damage produced by ethanol, perhaps via formation of protein adducts with subsequent autoantibody formation (55).

CYP2E1 Polymorphisms

The CYP2E1 gene is polymorphically distributed and 10 polymorphic loci on the human gene have been reported (56). No significant difference was observed in drinking behavior and susceptibility to alcohol in terms of frequencies of genotypes and alleles among Japanese subjects (57). To date, there does not appear to be any relationship between allelic forms of the CYP2E1 gene and the incidence of ethanol-related liver cirrhosis. No differences in gene expression were observed when reporter constructs of various CYP2E1 variant alleles were transfected into transformed cell lines (58). Many epidemiologic studies have been carried out to try to relate various CYP2E1 polymorphic alleles to numerous types of cancers (stomach, lung, colorectal, pancreatic, hepatic, renal, oral), but obvious and significant relationships have been difficult to observe (43).

Induction of CYP2E1

Many of the substrates of CYP2E1, e.g., ethanol, can induce their own metabolism (28, 29). In fact, these properties explain the ability of ethanol to inhibit the metabolism of certain substrates when the alcohol is present, i.e., ethanol and the substrate compete for oxidation by CYP2E1. However, ethanol can increase the metabolism of substrates when it is no longer present to compete, because the ethanol treatment already elevated the levels of the CYP2E1 catalyst. A variety of heterocyclic compounds such as imidazole, pyridine, pyrazole, 4-methylpyrazole (4-MP), thiazole, and isoniazid elevate CYP2E1 levels, as do solvents such as dimethyl sulfoxide, various alcohols, benzene and acetone (59, 60). Their mechanism of action will be discussed below.

CYP2E1 can also be induced under a variety of metabolic or nutritional conditions, e.g., in obese rats and in rats fed a high-fat diet (61). Somewhat paradoxically, levels of CYP2E1 in rats were also increased by fasting and by prolonged starvation (62). Diabetes increases CYP2E1 mRNA and protein levels severalfold (63). This may be related to the actions of insulin, which downregulated CYP2E1 expression at the post-transcriptional level in several studies (64, 65). CYP2E1 induction in diabetes may be associated with the elevated production of ketone bodies (66). The carbohydrate content of the diet influences CYP2E1 levels as high fat/low carbohydrate diets resulted in the highest levels of CYP2E1 induced by ethanol (67). In this respect, it is interesting that alcohol-induced liver damage is magnified in diets with very low levels of carbohydrate and high levels of fat (68). Hypophysectomy and triiodothyronine increase CYP2E1 mRNA and protein levels in contrast to insulin, which lowers them (69). In primary rat hepatocyte cultures, glucagon lowered CYP2E1 levels by accelerating turnover of the CYP2E1 protein by a cyclic adenosine monophosphate (AMP)-dependent process (70). Testosterone increased renal, but not hepatic, CYP2E1 levels (71).

Non-alcoholic steatohepatitis (NASH) is a condition characterized by hepatomegaly, elevated serum aminotransferase levels, and a histologic picture similar to that of alcoholic hepatitis. Oxidative stress and lipid peroxidation are critical factors involved in the genesis and probably the progression of NASH (72). In a mouse model of NASH, hepatic CYP2E1 was upregulated, and this was associated with a dramatic increase in lipid peroxide levels that were substantially inhibited by anti-CYP2E1 antibody (73). However, it is now recognized that NASH also develops in CYP2E1 knockout mice as other P450s, notably CYP4A10 and CYP4A14 are upregulated (73). An integrated concept according to which either CYP2E1 or CYP4A or both play key roles in ROS production and contribute centrally to the pathogenesis of NASH was recently proposed (74).

Regulation of CYP2E1 Expression

CYP2E1 is regulated by multiple, distinct regulatory mechanisms (58, 60, 75). The CYP2E1 gene is under transcriptional control during development. In rats, it is activated immediately after birth and is maximally transcribed within the first week. Upon fasting or induced diabetes, CYP2E1 mRNA is increased severalfold due to post-transcriptional mRNA stabilization (76). The regulation of CYP2E1 expression by diverse chemicals is less clear. At one fixed time point (24 h) after administration of ethanol, acetone or pyrazole to rats, Song et al. found that mRNA levels did not increase (59). The mechanism of induction was, therefore, suggested to be regulated at the level of protein degradation. From *in vivo* data of CYP2E1 turnover in rats chronically treated with acetone (77) and using *in vitro* hepatocyte culture systems (78, 79), exogenous CYP2E1 inducers such as acetone, ethanol, imidazole and 4-MP were shown to increase CYP2E1 by protein stabilization. Using *in vivo* radiolabeling of CYP2E1 followed by immunopurification, CYP2E1 was shown to be degraded in two phases with a short half-life of 7 h and a longer half-life of 37 h. However, after chronic acetone administration, the rapid phase of degradation was abolished, while the slower phase with the same half-life of 37 h was still observed. These data indicated that acetone, a substrate of CYP2E1, stabilizes the enzyme by inhibiting the rapid phase of its degradation (77).

Ethanol, at high concentrations (>65 mM) achieved by the intragastric infusion model, induced CYP2E1 transcriptionally (80). It is of interest to note that ethanol (up to 1.5 M concentration) did not change the level of CYP2E1 mRNA despite a 5-fold elevation of CYP2E1 protein and its activity in the FGC-4 hepatoma culture system (81). Roberts et al. (82) reported that ethanol increases CYP2E1 by protein stabilization in liver as well as extra-hepatic tissues such as kidney, brain and intestine. A turnover study, using *in vivo* radiolabeling of CYP2E1 with [^{14}C]NaHCO$_3$ and immunopurification, demonstrated that ethanol treatment, like acetone, abolished the rapid phase of CYP2E1 degradation while biphasic degradation of CYP2E1 was observed in the control animals (83). Pyrazole and 4-MP elevated liver and kidney CYP2E1 immunoreactive protein and catalytic activity in the absence of an increase in CYP2E1 mRNA levels (84, 85). In rat hepatocyte cultures, addition of pyrazole or 4-MP slowed the decline in CYP2E1 protein and activity, without any effect on CYP2E1 mRNA levels (79). Similarly, McGehee et al. (81) reported the half-life of CYP2E1 in the FGC-4 hepatoma cell line to be 1.8 h in the absence of ethanol and 45 h in the presence of ethanol. It is clear that a major mechanism of regulation of CYP2E1 formation appears to be post-transcriptional, as various substrates and ligands increase the content of CYP2E1 by protection against rapid degradation by intracellular proteolytic pathways.

In our laboratory, CYP2E1 degradation was also studied in HepG2 hepatoma cells that stably and constitutively express CYP2E1. When the cells were incubated for 2 days in the presence of CYP2E1 ligands such as ethanol, dimethyl sulfoxide, glycerol, pyrazole or 4-MP, CYP2E1 steady state levels were increased several-fold, as shown by immunoblot analysis and by enhanced oxidation of *p*-nitrophenol (86). Levels of CYP2E1 mRNA were not increased by the ligands. To evaluate CYP2E1 turnover in the HepG2 cells, pulse-chase experiments or studies with addition of cycloheximide to inhibit protein synthesis, followed by examination of the degradation rate of the remaining CYP2E1 protein, were carried out. The half-life of CYP2E1 was 3 h (pulse-chase) or 5 h (using cycloheximide) in the absence of ligand, whereas in its presence 60–80% of the original *p*-nitrophenol oxidation activity and CYP2E1 levels remained 24 h after addition of cycloheximide or after addition of an excess of cold methionine. These experiments suggest that ethanol and the other ligands elevate CYP2E1 levels by stabilizing the enzyme against rapid proteolysis.

CYP2E1 and the Proteasome Complex

What are the proteolytic systems responsible for CYP2E1 turnover and inhibited from their action on CYP2E1 by ethanol? Microsomes isolated from these cells showed a very slow rate of CYP2E1 degradation, suggesting that a protease in the ER is not a likely candidate for the rapid degradation of CYP2E1. Several inhibitors of lysosomal protease had little or no effect on CYP2E1 degradation. In order to evaluate a role for the proteasome complex in the degradation of CYP2E1, the effect of the substrate analogue Czb-Ile-Glu (OtBu)-Ala-Leucinal (PSI) on CYP2E1 degradation and content was determined. PSI inhibits the chymotrypsin-like activity of the proteasome. Calpeptin inhibitor, a peptidyl aldehydic nonproteasomal cytosolic protease inhibitor, was also evaluated to try to minimize the possibility of nonspecific effects by PSI. PSI proved to be effective in preventing CYP2E1 degradation, whereas calpeptin inhibitor provided little or no protection (86). PSI, added *in vitro* at concentrations up to 300 μM, had no effect on oxidation of 2,4-para-nitrophenol (PNP) by microsomes, suggesting that PSI was not acting as a ligand or substrate for CYP2E1. Theoretically, one consequence of diminishing the proteolytic degradation rate of CYP2E1 by PSI should be the steady state accumulation of CYP2E1 within the cells. Treatment of the HepG2 cells with PSI caused a concentration-dependent increase in levels of CYP2E1 apoprotein. Taken as a whole, these results indicate that human CYP2E1 has a short half-life span and that substrates can significantly modify its turnover rate in the intact cells. The proteasome proteolytic pathway appears to be involved in the degradation process of CYP2E1 in this model. Significantly, Bardag-Gorce et al. (87) recently showed that the rapid loss of CYP2E1, which occurs *in vivo* after the ethanol inducer is withdrawn, could be blocked by the proteasome inhibitor PS-341, thus establishing the critical role of the proteasome in regulating CYP2E1 turnover *in vivo*.

In view of the importance of the proteasome complex in the turnover of CYP2E1, the effect of chronic ethanol treatment on activity or content of the proteasome would be important to determine, since inhibition of this degradation complex would cause an increase in CYP2E1 levels. Studies by French and collaborators indeed showed that chronic ethanol administration in the intragastric infusion model produced a decrease in activity of the proteasome (88, 89). This inhibition may also cause oxidized, damaged proteins to accumulate in the liver and thereby contribute to ethanol-induced hepatomegaly. To specifically determine the role of CYP2E1 in the chronic ethanol-induced lowering of proteasome activity, CYP2E1 knockout mice were treated with ethanol; whereas ethanol lowered proteasomal activity in the wild type mice, activity was not affected in the CYP2E1-knockout mice (90). It was suggested that CYP2E1-dependent ROS production and lipid peroxidation may be responsible for the decrease in proteasome activity. We recently showed that in HepG2 cells that constitutively express CYP2E1, inhibition of the proteasome with lactacystin and other typical inhibitors potentiated the toxicity caused by addition of a polyunsaturated fatty acid, arachidonic acid, or by depletion of GSH (91). Potentiation of toxicity by the proteasome inhibitors was associated with an increased oxidative damage, as reflected by elevated lipid peroxidation, protein carbonyls and protein nitrotyrosine adducts, and the potentiation could be prevented by antioxidants. Lactacystin also potentiated arachidonic acid toxicity in hepatocytes isolated from pyrazole-treated rats with elevated levels of CYP2E1. Thus, the proteasome plays an important role in CYP2E1 turnover and removal of oxidized, damaged proteins, and subsequently in CYP2E1-mediated toxicity (92).

The CYP2E1 Knockout Mouse

The development of the CYP2E1 knockout mouse has been of great value in establishing the role of CYP2E1 in the toxicity of various hepatotoxins such as acetaminophen, benzene, acrylonitrile, and styrene (93–95). These mice have been used to validate the assumption that hydroxylation of *p*-nitrophenol may be used as a specific probe for CYP2E1 (96). Levels of acetone were strikingly elevated under fasting conditions in CYP2E1 null mice, suggesting the critical role of CYP2E1 in acetone metabolism (38). It has been reported that alcohol-induced liver damage occurred in CYP2E1 null mice to the same extent as in wild type controls, indicating that CYP2E1 does not play a role in alcohol liver injury (97). However, others have shown that ethanol-induced oxidative stress and inactivation of the proteasome complex was completely prevented in these mice (90). This is further discussed below. Recently, a CYP2E1-humanized transgenic mouse model that expresses functional and inducible human CYP2E1 was described (98). Comparisons between CYP2E1-humanized mice, CYP2E1 null mice and wild type mice will allow a determination whether actions of human CYP2E1 are similar to those of mouse CYP2E1 *in vivo*. Indeed, the CYP2E1-humanized mouse model was successfully used to characterize acetaminophen toxicity by human CYP2E1 (98).

CYP2E1 and Alcohol-Induced Liver Injury

Since CYP2E1 can generate ROS during its catalytic cycle, and its levels are elevated by chronic treatment with ethanol, CYP2E1 has been suggested as a major contributor to ethanol-induced oxidant stress and liver injury. In the intragastric model of ethanol feeding, large increases in microsomal lipid peroxidation have been observed, and the ethanol-induced liver pathology has been shown to correlate with CYP2E1 levels and elevated lipid peroxidation (18–20, 99, 100). Experimentally, a decrease in CYP2E1 induction was found to be associated with a reduction in alcohol-induced liver injury (101). CYP2E1 inhibitors such as diallyl sulfide (DAS) (99), phenethyl isothiocyanate (99) and chlormethiazole (102) blocked the lipid peroxidation and ameliorated the pathologic changes in ethanol-fed rats. Polyenylphosphatidylcholine, another compound exerting anti-CYP2E1 properties, was effective in opposing alcohol-induced oxidative stress (103). A CYP2E1 transgenic mouse model was developed that overexpressed CYP2E1. When treated with ethanol, the CYP2E1-overexpressing mice displayed higher transaminase levels and histological features of liver injury compared with the control mice (104).

On the other hand, studies by Thurman and colleagues at North Carolina have presented powerful support for a role for endotoxin, activation of Kupffer cells and production of cytokines such as tumor necrosis factor-α in the alcohol-induced liver injury found with the intragastric infusion model (22, 105). They suggested that CYP2E1 may not play a role in alcohol-induced liver damage, based upon studies with gadolinium chloride or CYP2E1 knockout mice (97, 106). However, in contrast to their observations, others have reported that gadolinium chloride does indeed decrease levels of several P450 enzymes including CYP2E1, and that it lowered the induction of CYP2E1 by ethanol (107, 108). Using the same knockout mice, Leclercq et al. (73) observed that other P450 forms, notably CYP4A10 and CYP4A14, were upregulated in the CYP2E1 knockout but not the wild type mice; these P450s were, like CYP2E1, active generators of ROS and catalysts of lipid peroxidation and, in the absence of CYP2E1, served as alternative initiators of oxidative stress. Activity of NADPH-cytochrome P450 reductase was elevated 2.5-fold by alcohol treatment in the CYP2E1 knockout mice; the reductase can generate ROS. Therefore, as discussed by Tsukamoto (109), induction by ethanol of other P450s or of the reductase in the CYP2E1 knockout mice might have served as alternative sources of oxidative stress in these mice, especially in the absence of CYP2E1. French and collaborators found that the ethanol-induced oxidative inactivation of the proteasome and increase in oxidized proteins (but not fatty liver) were completely prevented in the CYP2E1 knockout mice (90). Clearly, further studies are necessary to resolve the above discrepancies. It is likely that several mechanisms contribute to alcohol-induced liver injury, and that ethanol-derived oxidant stress is likely to arise from several sources, including CYP2E1, mitochondria and activated Kupffer cells. An important recent finding by the North Carolina group was that CYP2E1, but not NADPH oxidase, was required for ethanol-induced oxidative DNA damage in rodent liver (110). They concluded that while CYP2E1 may not be critical for ethanol-induced liver injury, it may play a role in ethanol-associated hepatocarcinogenesis (110).

Biochemical and Toxicological Properties of CYP2E1 in HepG2 Cells

An approach that our laboratory has utilized to try to define basic effects and actions of CYP2E1 is to establish cell lines that constitutively express human CYP2E1. HepG2 cell lines, which overexpress CYP2E1, were established either by retroviral infection methods (MV2E1-9 cells, or E9 cells) or by plasmid transfection methods (E47 cells) (111, 112). Hepatotoxins such as carbon tetrachloride or acetaminophen were more toxic in E9 cells than in control HepG2 cells, validating the utility of the model to study CYP2E1-dependent toxicity (113, 114). We have characterized the toxicity of ethanol, polyunsaturated fatty acids (PUFA) such as AA and iron in the E9 and E47 cell lines (27, 115–117). Concentrations of ethanol or AA or iron which were toxic to the CYP2E1-expressing cells had no effect on control HepG2 cells not expressing CYP2E1 or on HepG2 cells expressing a different P450, CYP3A4 (3A4 cells). Toxicity to CYP2E1-expressing cells was also found when GSH was depleted by treatment with L-buthionine sulfoximine (BSO) (118). Inhibitors of CYP2E1 prevented the toxicity by the above treatments. Antioxidants such as vitamin E, trolox and catalase also prevented toxicity. Treatment of CYP2E1-expressing cells with ethanol, AA, iron or BSO resulted in an increase in oxidative stress to the cells. In other studies, we observed that low concentrations of iron and AA that are not cytotoxic by themselves can act as priming or sensitizing factors for CYP2E1-dependent loss of viability in HepG2 cells and rat hepatocytes (119). The synergistic toxicity of AA plus iron was associated with elevated lipid peroxidation and could be prevented by antioxidants that prevent lipid peroxidation. Damage to mitochondria by CYP2E1-derived oxidants seems to be an early event in the overall pathway of cellular injury. Relatively low concentrations of iron and AA were effective in promoting toxicity to the CYP2E1-expressing cells, supporting the suggestion that interactions between

CYP2E1, iron and PUFA may lower the threshold concentrations for these reactive nutrients for inducing a state of oxidative stress. This stress may play a role in the development of alcohol-induced liver injury.

To extend the results with the HepG2 cells to primary cells, cultures of hepatocytes isolated from rats treated with pyrazole to elevate levels of CYP2E1 and from saline controls were exposed to the toxins described above, and toxicity was evaluated. Many of the basic findings described above for E9 and E47 cells were recapitulated in the hepatocytes from pyrazole-treated rats, i.e., AA or iron or AA plus iron were more toxic to pyrazole hepatocytes than saline control hepatocytes (120, 121). Ethanol was weakly toxic, but even this toxicity was greater in the pyrazole hepatocytes. Toxicity was associated with increased lipid peroxidation and could be prevented by antioxidants and the CYP2E1 inhibitor DAS.

Adaptation to oxidant stimuli is critical for short- and long-term survival of cells exposed to oxidative stress. While much of the focus on CYP2E1 has been from a toxicological point of view, the possibility that the hepatocyte attempts to respond to increased levels of CYP2E1 by upregulation of protective factors has not been studied. We found, to our surprise, that the E47 cells had higher GSH levels than CYP3A4-expressing HepG2 cells or control HepG2 cells (122). Increases in GSH were due to activation of the genes encoding the heavy (or catalytic) and light (or modulatory) subunits of glutamate-cysteine ligase (GCLC and GCLM, respectively). The increases in GCLC and GCLM mRNAs in the E47 cells were prevented by inhibitors of CYP2E1 and were also found in hepatocytes isolated from pyrazole-treated rats with elevated levels of CYP2E1 as compared to hepatocytes from saline-treated control rats (122, 123). The increases in GSH and GCLC and GCLM mRNAs were also prevented by antioxidants, suggesting that ROS generated by CYP2E1 were responsible for the upregulation of these antioxidant genes. The GCLC transcriptional upregulation mediated by CYP2E1-derived ROS seems to operate through a redox-sensitive element (ARE4) localized 3.1 kb upstream of the transcription start site in the GCLC gene (123). There was also a twofold increase in the content and activity of catalase, cytosolic glutathione *S*-transferase and microsomal glutathione *S*-transferase in the E47 cells due to activation of their respective genes (124). These activations in the E47 cells were prevented by antioxidants, suggesting that ROS generated by CYP2E1 were also responsible for the induction of these antioxidant enzymes. Indeed, the E47 cells, because of the activation of a variety of antioxidant genes, were less sensitive to toxicity by exogenously added H_2O_2, menadione or 4-hydroxynonenal than were control cells. We believe that the upregulation of diverse antioxidant genes may reflect an adaptive mechanism to remove CYP2E1-derived oxidants.

Hepatic stellate cells (HSC) are central to the fibrotic response of the liver to injury, and ROS activate stellate cells. Since CYP2E1 produces ROS, ethanol-induced CYP2E1 expression may promote collagen type I biosynthesis by stellate cells. However, CYP2E1 is mostly present in hepatocytes, whereas stellate cells contain low levels of CYP2E1. Accordingly, a coculture model involving HepG2 cells and stellate cells was developed (125, 126), in which the HepG2 cells and the stellate cells were separated from each other by an insert; therefore, the experimental protocol was designed to evaluate whether mediators (ROS, cytokines, growth factors) produced by HepG2 cells diffuse to the HSC and affect collagen type I protein levels. There was a time-dependent increase in collagen type I when stellate cells were coincubated with C34 control cells, which was further elevated when stellate cells were coincubated with CYP2E1-overexpressing E47 cells. E47 plus stellate cell cocultures secreted much more type I collagen protein. These experiments suggest that CYP2E1-overexpressing E47 cells generate diffusible mediators that promote type I collagen synthesis and release by stellate cells. Catalase and vitamin E markedly decreased type I collagen synthesis by both cocultures and completely blocked the increased collagen production by the E47 coculture. These results suggest that E47 cells release ROS, such as H_2O_2 and lipid peroxidation products, that stimulate type I collagen synthesis by stellate cells.

Damage to the mitochondria may represent a common early event in cell injury caused by toxic agents (127). Mitochondrial damage is initially manifested by a decrease in mitochondrial membrane potential ($\Delta\psi_m$) followed by ATP depletion (128, 129). $\Delta\psi_m$ was assessed by flow cytometry after double staining with rhodamine 123 and propidium iodide. Exposure of E47 cells to BSO (130), AA (131), or AA plus iron (119) increased the percentage of cells that showed low rhodamine 123 fluorescence but were not stained with propidium iodide. This population consists of cells that are still viable but with damaged mitochondria, which shows that in the CYP2E1-dependent models of toxicity mitochondria are affected before the onset of cell death (i.e., an early event). This early mitochondrial damage was prevented by antioxidants, linking oxidative stress to mitochondrial damage. That mitochondria are an important target for CYP2E1-mediated oxidative stress is suggested by the fact that overexpression of mitochondrial catalase is capable of protecting cells that overexpress CYP2E1 against the toxicity induced by BSO, AA, or AA plus iron (130, 132, 133). If the decrease of $\Delta\psi_m$ depends on the opening of the permeability transition pore, then a specific inhibitor of the permeability transition should decrease the loss of $\Delta\psi_m$ induced by the toxic agents. Cyclosporine A inhibited the loss of $\Delta\psi_m$ and the toxicity in CYP2E1-expressing cells exposed to AA, AA plus iron, or BSO (119, 121, 133), suggesting a role for the permeability transition in mitochondrial depolarization and subsequent toxicity. Additional evidence for increased mitochondrial damage in CYP2E1-overexpressing cells is that depletion of GSH decreased oxygen uptake with several respiratory substrates in permeabilized E47 cells, and vitamin E prevented this decrease (112). Damage to mitochondria is an important event in the CYP2E1-dependent toxicity.

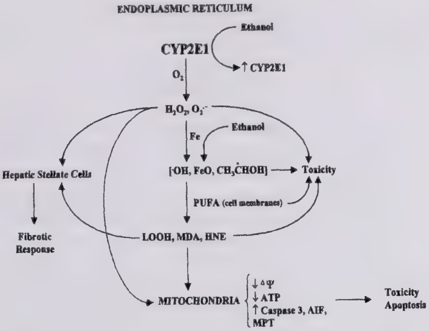

Figure. Working model for CYP2E1-dependent oxidative stress and toxicity. Please see text for explanation.
$O_2^{\cdot -}$ = superoxide anion radical; Fe = iron; ·OH = hydroxyl radical; FeO = perferryl radical; $CH_3C{\cdot}HOH$ = 1-hydroxyethyl radical; PUFA = polyunsaturated fatty acids; LOOH = lipid hydroperoxides; MDA = malondialdehyde; HNE = 4-hydroxynonenal; AIF = apoptotic inducing factor; MTP = mitochondrial permeability transition.

Conclusions

This review describes the biochemical and toxicological properties of CYP2E1, including its role in ethanol oxidation, its cellular localization, its effective metabolic substrates, its induction by ethanol and by various other compounds and in certain pathophysiological conditions, and how levels of CYP2E1 are regulated. CYP2E1 is of special interest since it activates a variety of compounds to reactive intermediates that produce tissue damage. CYP2E1 also metabolizes procarcinogens to the ultimate carcinogen. CYP2E1 is an active producer of ROS, which are generated during its catalytic cycle even in the absence of substrate. This process, plus the induction of CYP2E1 by ethanol, has led to many studies on the role of CYP2E1-mediated oxidant stress in alcohol-induced hepatic injury. Ethanol is also a substrate for CYP2E1, producing reactive products such as acetaldehyde and the 1-hydroxyethyl radical, which may contribute to alcohol-induced liver damage. To further study the properties of CYP2E1, our laboratory developed HepG2 cell lines which express human CYP2E1 and evaluated the CYP2E1-related oxidative stress and cellular toxicity produced when ethanol, BSO, iron, or AA were added to the culture medium.

A working model of CYP2E1-dependent oxidative stress and toxicity is shown in the figure. Ethanol increases levels of CYP2E1, largely by a post-transcriptional mechanism involving enzyme stabilization against degradation. CYP2E1, a loosely coupled enzyme, generates ROS such as $O_2^{\cdot -}$ and H_2O_2 during its catalytic cycle. In the presence of iron, which is increased after ethanol treatment, more powerful oxidants including ·OH, ferryl species, and 1-hydroxyethyl radical are produced. Initially, the liver cells respond to the CYP2E1-related oxidative stress by transcriptionally inducing various antioxidant enzymes. Ultimately, these protective mechanisms are overwhelmed and the cells become sensitive to the CYP2E1-generated oxidants. These various oxidants can promote toxicity by protein oxidation and enzyme inactivation, oxidative damage to the DNA, and disturbance of cell membranes via lipid peroxidation and production of reactive lipid aldehydes, such as malondialdehyde and 4-hydroxynonenal. Mitochondria appear to be among the critical cellular organelles damaged by CYP2E1-derived oxidants. A decrease of $\Delta\psi_m$ probably due to the mitochondrial membrane permeability transition causes release of proapoptotic factors resulting in apoptosis. Decrease in ATP levels will cause necrosis. Some CYP2E1-derived reactive oxygen species, e.g., H_2O_2, lipid hydroperoxides (LOOH), malondialdehyde (MDA), 4-hydroxynonenal (HNE), are diffusible and may exit hepatocytes and enter other liver cell types such as stellate cells, and stimulate these cells to produce collagen and elicit a fibrotic response. We believe that the linkage between CYP2E1-dependent oxidative stress, mitochondrial injury, stellate cell activation and GSH homeostasis contributes to the toxic actions of ethanol on the liver.

Future Perspectives

Alcohol-induced liver injury is probably a multifactorial process involving several mechanisms. Future studies are required to further clarify how alcohol produces oxidative stress in various tissues. Some of the major proposed systems require more detail about mechanism, e.g., how ethanol-derived NADH, itself or when reoxidized in the mitochondrial respiratory chain, produces ROS. What is the role of ethanol metabolism or ethanol metabolites such as acetaldehyde in the production of ROS, and how is oxidative stress produced by ethanol in tissues with limited ethanol metabolism? What are the priming or sensitizing factors for ethanol-induced oxidant stress and cell injury? Can markers predictive of individuals particularly sensitive to ethanol-induced oxidant stress and liver injury be developed?

The role of CYP2E1 in the toxic effects of ethanol requires further study, as this remains a controversial issue. The question is significant not only from a mechanistic point of view but perhaps also from a therapeutic treatment one. If indeed CYP2E1-induced oxidative stress plays a central role in alcohol-induced hepatic damage, possible strategies for preventing this stress may be effective in attempts to minimize the hepatotoxicity of ethanol in humans. The CYP2E1 inhibitors that were partially effective in preventing ethanol-induced liver injury are not entirely selective and may be toxic. There is a need for the development of selective, non-toxic inhibitors of CYP2E1 that could be used *in vivo*. Inhibitors such as phenylisothiocyanate, diethyldithiocarbamate and DAS are often toxic at concentrations needed to inhibit CYP2E1, especially *in vivo*. They are also not selective, as they can function as antioxidants or have other actions, e.g., DAS can induce heme oxygenase-1 (134). *S*-adenosyl-L-methionine is hepatoprotective against several toxins and can inhibit CYP2E1; however, the K_I for inhibiting CYP2E1 is high, so *S*-adenosyl-L-methionine is not likely to be an effective inhibitor of CYP2E1 *in vivo* (135). YH439 is a novel synthetic compound inhibiting CYP2E1 (but also other P450s), which is currently being evaluated as a hepatoprotective agent (136, 137). Actually, natural agents inhibiting CYP2E1, including DAS (from garlic) mentioned above, phenylethyl isothiocyanate and sulforaphane (present in cruciferous vegetables) (138) and bergamottin (found in the essential oils of grapefruit and orange) (139) have been proposed to be used at low non-toxic concentrations as possible candidates for minimizing the ethanol-induced hepatotoxicity (140).

The regulation of CYP2E1 protein levels is complex, when observed at the transcriptional and post-transcriptional levels; more mechanistic details as to how ethanol modulates CYP2E1 levels would be helpful, e.g., effects on activity of the proteasome, ubiquitination, how ethanol stabilizes CYP2E1. What are the factors that trigger the rapid turnover of CYP2E1? This is a key question for understanding why CYP2E1 turns over so rapidly. Chronic ethanol treatment decreases activity of the proteasome (90, 141); is this part of the mechanism by which ethanol increases the content of CYP2E1? Is ubiquitination of CYP2E1 required for its degradation by the proteasome (142)? The answer to this is not clear, and has important implications with respect to the mechanism of CYP2E1 turnover, the role of the 20S vs. the 26S proteasome complex, the role of accessory chaperones, e.g., heat shock proteins (143), how ethanol and other low-molecular ligands act to stabilize CYP2E1, e.g., preventing labilization, ubiquitination, access to the proteasome core.

Most information on the biochemical and pharmacological actions of CYP2E1 is derived from studies with rodents and rabbits, and cultured hepatocytes; extrapolation to human studies will obviously be necessary. A major advance in this direction will be the humanized CYP2E1 transgenic mouse model (98). The role of polymorphic forms of CYP2E1 on its expression, activity, and actions requires further understanding, as current literature suggests some possible relationships with certain types of cancers, but not with alcohol toxicity. Are there other endogenous substrates for CYP2E1? At present, acetone and some fatty acids (ω-hydroxylation catalyzed by CYP2E1) appear to be physiological substrates for CYP2E1, but further study should be carried out, because altered metabolism of such putative endogenous substrates, if any, could contribute to the cellular actions associated with activated CYP2E1. CYP2E1 is present, although at relatively low levels, in other tissues, e.g., kidney, lung, brain, gastrointestinal tract. Much less is known about the actions of CYP2E1 under various pathophysiological conditions or after chronic ethanol exposure in these tissues. There is much current interest in synergistic interactions between alcohol and hepatitis B or hepatitis C virus, especially with respect to generating oxidative stress. The role of CYP2E1 in such synergistic interactions (144), would be important to explore in view of the many chemicals and conditions that are known to elevate CYP2E1.

The ability of alcohol to promote oxidative stress and the role of free radicals in alcohol-induced tissue injury clearly are important areas of research, particularly because such information may be of major therapeutic significance in attempts to prevent or ameliorate alcohol's toxic effects, e.g., by antioxidants, iron chelators, inhibitors of CYP2E1 or of cytokine production/actions, and GSH replenishment. As basic information continues to emerge regarding the role of oxidative stress in disease development and the mechanisms underlying ROS-related cellular toxicity, these findings will lead to more rational antioxidant therapeutic approaches. Moreover, these findings could result in the development of more effective and selective new medications capable of blocking the actions of ROS and, consequently, the toxic effects of alcohol.

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Dean's Lecture

The Use of Receptor-Specific Antibodies to Study G-Protein-Coupled Receptors

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Abstract

The identification of G-protein-coupled receptor (GPCR) cDNAs has facilitated a number of studies characterizing the biochemical properties of the receptor protein. Most of these studies have used antibodies directed against the epitope-tagged receptor expressed in heterologous cells, because of the lack of sensitive and selective antibodies capable of recognizing endogenous receptors in their native state. In order to facilitate studies with endogenous receptors, efforts have been made to generate receptor-type selective, sensitive antibodies that are able to recognize endogenous receptors. In this review, we discuss the strategies as well as the details of the techniques used for the generation of monoclonal and polyclonal antibodies with a focus on family A GPCRs.

Key Words: Opiate, opioid receptors, morphine, monoclonal.

Introduction

G-PROTEIN-COUPLED RECEPTORS (GPCRs) comprise the largest family of cell surface receptors and are characterized by the presence of seven transmembrane domains. This superfamily can be subdivided into three major subfamilies: family A (rhodopsin-like/beta adrenergic receptor family) characterized by relatively short N- and C-terminal regions; family B (glucagon-like/secretin-like) characterized by a large N-terminal region with multiple cysteines; and family C (metabotropic glutamate-like) characterized by a very large N-terminal region. Among these, family A is by far the largest and exhibits many of the structural features conserved in other GPCRs, such as the consensus sequence for N-linked glycosylation sites near the amino terminus, a palmitoylation site in the C-terminal tail, and phosphorylation sites in the first and third intracellular domains as well as in the C-terminal tail (1). These receptors also elicit a wide range of responses (2–4). Recently it has been shown that family A GPCRs can associate with each other as well as with other GPCRs, leading to the modulation of their pharmacological, functional and trafficking properties (5–7).

Studies examining the biochemical and cell biological properties of endogenous receptors have been hampered by a lack of sensitive and selective antibodies that are able to recognize native receptors in live or fixed cells. To date, studies characterizing the biochemical properties of GPCRs have made use of the availability of receptor cDNAs to introduce an epitope tag at the N-terminus. Antibodies directed against this tag are then used to investigate epitope-tagged receptors expressed in heterologous cells. In order to study endogenous receptors in their native environment, antibodies would be useful. Receptor-type specific antibodies can be generated to peptides derived from the N-terminal region, which is relatively diverse between closely related receptors. A comparison of the N-terminal region of the three types of opioid receptors (μ, δ, κ) reveals significant differences that can be employed to generate receptor type specific antibodies. In this article we describe strategies that can be used in the generation and characterization of GPCR-type selective antisera.

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Methods

Generation of the Antibodies

Polyclonal antibodies in rats. The generation of polyclonal antibodies to a given antigen, such as a GPCR, is less time-consuming and labor intensive compared to the generation of monoclonal antibodies. In addition, it has other advantages, such as recognition of a mixture of epitopes on the antigen, which makes it less sensitive to changes in the nature of the antigen, such as polymerization or denaturation. The concentration of specific polyclonal antibodies in the serum is between 0.05 and 0.2 mg/mL, and in some instances it can be as high as 1 – 3 mg/mL. Polyclonal antibodies can be grown in animals as diverse as rats, goats, rabbits, etc. Here we describe the generation of polyclonal antibodies to opioid receptors in rats, a choice that has several advantages such as ease in handling the animals, low cost and relatively short time requirement.

Immunogen preparation: In order to raise polyclonal antibodies to GPCRs, antigenic peptides have to be generated to regions that are diverse when considering closely related GPCRs. For example, in the case of opioid receptors, the following sequences can be selected: amino acid residues 14 – 30 from mouse μ opioid receptor, 3 – 17 from mouse δ opioid receptor and 2 – 18 from rat κ opioid receptor. Antigenic peptides can be commercially synthesized on a multiple antigenic peptide (MAP) backbone (Research Genetics, Huntsville, AL) or conjugated to bovine serum albumin (BSA). When using MAP peptides, the immunogen is prepared by dissolving 1 mg of MAP peptide in 1 mL of sterile phosphate-buffered saline (PBS). In order to conjugate an antigenic peptide with BSA, 2 mg of the peptide and 10 mg of BSA are dissolved separately in 0.5 mL of PBS. The two solutions are mixed and transferred to a tube containing 10 mg EDC [1- ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride] and mixed overnight at 4°C. The mixture is dialyzed against sterile deionized water for 24 h, and the dialyzate is concentrated using a Micron-30 column (Millipore Corporation, Bedford, MA) at 4°C. The retentate is diluted in 50 mM phosphate buffer (pH 7.2) to achieve a final concentration of the antigen of approximately 20 μg/μL. Aliquots (50 μL) are stored at – 80°C till use.

Emulsion preparation: Approximately 0.3 mL Freund's adjuvant (complete or incomplete; GIBCO, Irvington, Carlsbad, CA) is mixed with 0.3 mL PBS containing antigen (either the MAP or the BSA conjugated peptide) in an eppendorf tube and passed through an insulin syringe ten times. The mixture is mixed at 4°C at moderate speed for 20 min in a rotating shaker and passed through the syringe till emulsified. Emulsification is verified by placing a drop of the emulsion in 10 mL of water in a Petri dish. If the emulsification is incomplete, the drop will disperse in the water. If it does, the emulsification procedure is repeated as described above.

Serum preparation: The preimmune serum is collected prior to immunization. For this, Sprague-Dawley rats (200 – 250 g / male and approximately two months old) are placed in a small restraining cage or container. Their tails are warmed with an infrared lamp or hot water (50 – 60°C) to increase the flow of blood to the tails; the temperature should not hurt the animals (if it is too hot for the experimenter's hand, then it is too hot for the rats). A small incision is made at the tip of the tail and blood is collected (the bleeding will stop spontaneously). The preimmune serum is prepared (as described below) and stored in aliquots at – 20°C till use (as control).

For serum preparation, the blood is allowed to clot for 30 – 60 min at 37°C for 2 h at room temperature, the clot is separated from the sides of the tube using a Pasteur pipette and the tube is kept at 4°C overnight to allow the clot to contract. The serum is collected by centrifugation at 10,000 × g for 10 min at 4°C and stored in aliquots (1 mL) at – 20°C till use. The working stock is prepared by adding 50 μL of 0.5 M EDTA (pH 7.4) and 2 μL of 50% thimerosal and kept at 4°C.

Injection schedule: For the initial injection, Freund's complete adjuvant is used, and for boosters an emulsion in Freund's incomplete adjuvant is used. Two booster injections are given every three weeks, and the animals are sacrificed a week after the second booster injection.

Monoclonal antibodies. The advantages of generating monoclonal antibodies are that they recognize a single epitope on the antigen, can be generated against complex mixtures of epitopes, are homogenous with respect to immunoglobulin subtype, and give highly reproducible results.

Preparation of antigen and injection: MAPs or peptides conjugated to BSA are emulsified in Freund's complete adjuvant, as described in the "**Generation of the Antibodies—Polyclonal antibodies in rats**" section above. Approximately 10 μg of each emulsified peptide is injected intraperitoneally into Balb/c mice

(6-week-old female). Every 15 days, booster injections are given with 10 μg of antigen emulsified in Freund's incomplete adjuvant. Antibody production is monitored by ELISA (described below in the "**Characterization of the Antibodies—ELISA**" section) using blood collected from the tail of these mice as described earlier in the "**Generation of the Antibodies—Polyclonal—*Serum preparation***" section.

Hybridoma generation: Mice producing the highest titer of antisera are given a booster injection of 50 μg of MAPs (or peptides conjugated to BSA) intravenously. Three days later the spleen is removed, splenocytes are prepared and 1×10^8 splenocytes are fused with 1×10^7 SP2/0-Ag-14 myeloma cells using PEG-1000, as described by Kohler and Milstein (8) and Gomes et al. (9). The cells are plated into 24-well plates in a hypoxanthine, aminopterin, thymidine (HAT) selection medium and allowed to grow for 15 days. The hybridoma-secreting clones are screened by ELISA as described below and sub-cloned by limiting dilution to achieve a single cell/well of a 96 well plate.

Purification and subtyping: The hybridoma supernatant is subjected to affinity purification using protein A-Sepharose CL-4B beads as described by Ey et al. (10). Fractions containing immunoglobulin are identified by absorbance at 280 nm, and protein concentration is determined by the method of Bradford (11). Purified antibodies are isotyped using an antibody isotyping kit as per manufacturer's instructions (Sigma Chemical Company, St. Louis, MO).

Large scale preparation:

1. Tissue culture: The simplest large scale method is to grow hybridomas in large tissue culture flasks (Integra Celline 1000, Integra Biosciences AG, Switzerland) and collect the supernatant according to the manufacturer's protocol. This will yield approximately 10 μg antibodies/mL of supernatant.
2. Production of ascites: Another method for obtaining a large quantity of antibodies is by producing ascites. For this, each animal is injected intraperitoneally (i.p.) with 0.5 mL of Pristane (2,6,10,14-tetramethylpentadecane). Seven days after the first Pristane injection, the cultured hybridoma cells are harvested, and centrifuged, and the supernatant is discarded. The pellet is resuspended in sterile PBS to a concentration of approximately $2-20 \times 10^6$ cells/mL. Approximately 0.5 mL of the cell suspension is injected i.p. into each animal using a 21 G needle. Care must be taken to ensure that the animal is not in serious discomfort. When there is swelling of the abdomen (indicating ascitic fluid production), the animal is sacrificed, and the ascitic fluid is collected using a syringe with a 19 G needle and transferred to a 10 mL tube. Cells are removed by centrifugation for 10 min at 250 × g. The supernatant is frozen in small aliquots. The cells can be used to inoculate another animal or frozen in liquid nitrogen for future inoculation. This procedure can give approximately 10 mg/mL of antibodies.

Problems and troubleshooting: The most common problem during monoclonal antibody production is that of contamination. Even with the most extensive precautions, occasionally some contamination will occur; the most common types of contamination and methods of treatment are described below.

1. Bacteria: These are seen under the light microscope as rods or cocci and can be treated with antibiotics. If the growth media already contains penicillin and streptomycin, then 50 μg/mL gentamycin can be added. Alternatively, cells can be sub-cloned into media containing antibiotics in an effort to dilute out the bacteria. However, it is best to discard the contaminated cells and sterilize the contaminated wells with 70% ethanol.
2. Fungi: These are easy to see under the microscope as thin strands of hyphae. Fungal growth can be prevented by addition of fungizone (2.5 μg/mL) to the growth media. However, once fungal contamination appears, it is best to discard the cells and sterilize the wells, because it can spread quickly to adjacent wells. Wells are sterilized by removing the media by suction, carefully avoiding touching adjacent wells, adding Chloros (sodium hypochlorite) for 2–3 min, rinsing with sterile water and leaving the wells empty. In addition, the lid of the plate should be replaced to minimize the possibility of further contamination.
3. Yeast: These are easily recognizable under the light microscope as budding microorganisms. Yeast infection can be prevented by treatment with fungizone. However, once yeast contamination is detected in a well, it is best to discard the supernatant and sterilize the well, as described above for fungal contamination.
4. Mycoplasma: This contamination is difficult to diagnose, as the organisms cannot be seen under the light microscope, but typically they slow down cell growth. It is possible to rescue cells contaminated with mycoplasma by treat-

ing them with a mycoplasma removal agent (ICN Biomedicals, Inc., Costa Mesa, CA) according to the manufacturer's protocol.

Characterization of the Antibodies

Enzyme-linked immunosorbent assay (ELISA) is commonly used to screen and characterize the antibody specificity to the antigen. The antigen could be the immunogenic peptide itself or cells expressing the GPCR containing the immunogenic peptide. Appropriate controls are untreated peptides or cells expressing closely related GPCRs. Antigens are coated on the ELISA plate, and the hybridoma supernatant is used as a primary antibody. Several dilutions of primary or secondary antibody (horseradish peroxidase [HRP] conjugated) are used to assess the specificity of the interaction. We will describe in this section the different types of ELISA assays that can be performed using the monoclonal or polyclonal antibodies.

Enzyme-Linked Immunosorbent Assay (ELISA)

Peptide antigens. For routine screening of hybridoma supernatants the antigen (1 μg of the MAPs peptide in 50 μL PBS) is added to each well of an ELISA plate (96 well plate Flat-bottom Immuno plate, Nalge Nunc International, Rochester, NY) and allowed to air dry. Non-specific sites are blocked with 3% BSA (Sigma) in PBS for 1 h at 37°C. Wells are incubated with the hybridoma supernatant at 4°C for 16 – 18 h, washed 4 times with PBS, and incubated with peroxidase conjugated anti-mouse antibody (1:1000 in PBS) for 1 h at 37°C. Wells are washed 4 times with PBS followed by a 5 min incubation at room temperature with 100 μL of substrate (0.5 mg/10 mL of ortho-phenylenediamine in 0.15 M citrate-phosphate buffer, pH 5 containing 10 μL of H_2O_2). The reaction is terminated by the addition of 50 μL of 5N H_2SO_4 and the color is quantitated at 490 nm in an ELISA reader (Bio-Rad model 550; Bio-Rad Laboratories, Inc., Hercules, CA).

Cells in 24 well plates. For examining specificity and sensitivity of antibodies, cells that are untransfected or transfected with specific or closely related receptors are used for whole cell ELISA. Cell lines generally used for transfection include CHO (Chinese hamster ovary), COS (Simian kidney cells that are SV40 transformed) and HEK-293 (Human embryonic kidney). Cells are transfected with the receptors of interest using Lipofectamine 2000 reagent according to manufacturer's protocol (Invitrogen, Carlsbad, CA). After 48 h, approximately 2 × 10^5 cells/well are plated onto a 24-well plate previously treated with poly-L-lysine. The medium is removed after 24 h (when the cells have attached), wells rinsed with PBS, and cells fixed with ice cold 100% methanol (at – 20°C) for 8 – 10 min or 4% paraformaldehyde for 10 min (at 4°C). The wells are washed twice with PBS, and non-specific sites are blocked with 3% BSA in PBS for 1 h at 37°C. The wells are then incubated with the primary antibody (either monoclonal or polyclonal; 1:1000) at 4°C for 16 – 18 h. Next the wells are washed 4 times with PBS and incubated with peroxidase conjugated anti-rat or anti-mouse (1:1000; Vector Laboratories, Inc., Burlingame, CA) antibody in PBS for 90 min at 37°C. Finally, the wells are washed and antibody binding is determined as described above ("**Characterization of the Antibodies — ELISA — Peptide antigens**" section).

Cells in 96 well plates. For studies involving the screening of multiple samples, 96 well plates can be prepared and stored at 4°C. Cells heterologously expressing the receptor of interest or neuroblastoma cells that endogenously express the receptors are plated (1 × 10^5 cells/well in PBS buffer). We routinely use SK-N-SH, a human neuroblastoma cell line that expresses many family A GPCRs. Wells are air-dried using a commercial convection fan, sealed and kept at 4°C till use. ELISA is carried out as described above.

ELISA with membranes in 96 wells. For studies examining receptor expression in endogenous tissue, membranes are prepared either from cells expressing receptors or from endogenous tissues, as described elsewhere (12). Each well of an ELISA plate is coated with 10 μg of membrane protein, and the plates are air dried as described above ("**Characterization of the Antibodies — ELISA — Cells in 96 well plates**" section) and stored at 4°C till use. ELISA is carried out as described above.

ELISA with membranes in tubes. If the antibodies are sensitive to methanol fixation or air-drying, the assay can be carried out in tubes. Membranes from cells expressing receptors or from endogenous tissues are prepared as described by Gomes et al. (12). Then 10 μg of membranes are placed in eppendorf tubes (and 100 – 200 μg of HEK-293 cell membranes are added to the tubes as bulk for visualization). The same amount of HEK membrane protein is used as negative control. ELISA is performed as described above, except that membranes are not fixed with methanol and all of the washes are carried out by centrifugation at 3000 rpm for 3 – 5 min. Extreme caution must be exercised so as not to lose the sample between washes (narrow gel loading tips help in this regard).

Section ELISA. Section ELISA can be used to determine if the antibodies recognize endogenous receptors in tissue sections, and to compare region-specific differences in receptor expression. For this, brains are collected and dissected into different regions and are immediately frozen at –80°C till use. Frozen brain regions are embedded in M-1 Embedding Matrix (Thermo Electron Corporation, Pittsburgh, PA) and 10 μm serial sections are cut using a MICROM HM 560 CryoStar (Richard-Allan Scientific, Kalamazoo, MI). Two sections from each region are placed on Fisher Brand Superfrost Plus slides (Fisher Scientific Research, Morris Plains, NJ) and circled immediately with ImmEdge PAP pen (Vector) to form a waterproof barrier; the resulting wells hold an approximately 200 μL solution. ELISA is performed in these wells using the same protocol as described above. The reaction product is then transferred to wells of 96 well plates, and absorbance at 490 nm is measured with a Bio-Rad ELISA reader.

Problems and troubleshooting: Problems commonly encountered during the ELISA assays are elevated background, poor signal or absence of a signal. These could be due to:

1. Inadequate washing and draining of wells: This can be addressed by draining the wells by completely inverting the plate on absorbent tissue at the end of each wash. And tapping the plate repeatedly to remove residual solution also helps.
2. Contamination of substrate solution with metal ions or oxidizing reagents: This can be avoided by using only distilled/deionized water in the preparation of the various solutions and by using clean plasticware.
3. Substrate exposed to light prior to use also leads to poor signal. Substrate should be freshly prepared about 10 min before use and should be kept in the dark till use (covering the tube with aluminum foil might help).
4. Evaporation of reagent from wells during incubation: To prevent the evaporation of reagents during incubation with primary and secondary antibodies, ELISA plates should be covered with a plastic lid.

Immunoprecipitation and Western Blotting

Immunoprecipitation of receptors from cells and tissues. Antibodies can be used to immunoprecipitate GPCRs from cells or tissues. For immunoprecipitation of opioid receptors we use HEK-293 cells, untransfected or transfected with Flag tagged μ, δ or κ opioid receptors, and solubilize them as described by Jordan and Devi (13). Briefly, cells are lysed for 1 h in NP-40 lysis buffer (150 mM NaCl, 1 mM EDTA, 10% glycerol, and 1 mM $CaCl_2$) containing 10 mM iodoacetamide and protease inhibitor cocktail (Sigma), and 100–200 μg of solubilized protein is incubated with 1–2 μg of receptor-specific monoclonal antibody overnight at 4°C. Immunocomplexes are isolated by incubation with 10% v/v protein A-Sepharose beads for 2–3 h. The beads are washed 3 times with NP-40 lysis buffer and resuspended in sample buffer followed by heating at 60°C for 15–30 min to release the immunoprecipitated receptor into the sample buffer. The mixture is centrifuged at 10,000 rpm for 20 min, and the supernatant is resolved under reducing or non-reducing conditions on 8% SDS-PAGE. Gels are transferred to 0.2 μm nitrocellulose membranes, blocked in 5% non-fat dried milk in TTBS (50 mM Tris-Cl, 150 mM NaCl, 0.1% Tween-20), and incubated with polyclonal anti-Flag antibody (1:5000 in TTBS) for 2 h at room temperature. The membranes are washed 6 times (5 min each) in TTBS followed by incubation with anti-rabbit HRP conjugated polyclonal antibody (1:5000 in TTBS) for 1 h at room temperature. The membranes are then washed 6 times with TTBS and treated with SuperSignal (Pierce Biotechnology Inc., Rockford, IL) for 3 min followed by exposure to X-ray films (Eastman Kodak, Rochester, NY) for different time periods to obtain multiple exposures that differ in the intensity of signal.

***Problems and troubleshooting*:** Two major problems during immunoprecipitation are blank blots or the presence of multiple bands on the blot. There are several possible reasons:

1. The antigen is not detected because of its small size, leading to transfer through the membrane. This can be prevented by reducing the transfer time and/or using a 0.20 μm nitrocellulose membrane to trap the antigen (larger antigens would not be transferred under these conditions). To ensure that the transfer is complete, gel is stained with Coomassie blue, or the nitrocellulose membrane is stained with Ponceau S. If the antigen is not detected because of its large size, the transfer time is increased. Adding SDS to the transfer buffer or decreasing the methanol concentration in the transfer buffer also helps. It is also possible that the lack of signal is due to insufficient amount of antigen in the sample in which case the amount of sample, loaded on the gel should be increased.
2. Bands corresponding to the antigenic protein are not detected. This could be due to incomplete dissociation of immunoprecipitated material from the protein A-Sepharose beads,

in which case the time of heating with the sample buffer is increased. The temperature is increased to about 80ºC, or 8M urea is used in the sample buffer. Alternatively, this could be due to the presence of large amounts of unrelated protein in the immunoprecipitate, in which case the protein A-Sepharose beads should be washed under more stringent buffer conditions such as higher salt and/or detergent concentration.

3. If the specific signal detected in the blot appears in the form of a smear, the amount of protein loaded on the gel can be decreased.

Flow Cytometry

Flow cytometry is used to characterize cell surface antigens, since this technique provides useful data for identifying and separating cell populations with different levels of receptor expression.

Analysis of cells. For this, approximately 3 ×10^5 cells/well are plated onto a 24 well plate, and the wells are washed with 0.5 ml of PBS. The cells are incubated with primary antibodies in 50% fetal bovine serum (FBS) in PBS at 4ºC for 16 h, washed 3 times with 0.5 mL of 1% FBS in PBS and incubated with Alexa 488-conjugated goat anti-mouse/anti-rat IgG (1:400 in 50% FBS in PBS) for 2 h at 4ºC. The wells are washed 3 times with 1% FBS in PBS and 3 times with PBS followed by 10 min incubation at 37°C with 250 μL of 1% edetic acid (EDTA) in PBS. The cells are collected into tubes containing 25 μL of 37% formaldehyde (care should be taken to ensure a single cell suspension by up and down pipetting), lightly vortexed and subjected to fluorescent-activated cell sorter (FACS) analysis (14) using a FACScan flow cytometer (Becton Dickinson Immunocytometry, Inc., Mountain View, CA).

***Problems and troubleshooting*:** A common problem with FACS analysis is a weak signal, which could be due to a low expression of the antigen at cell surface, insufficient amount of primary antibody, or high background.

1. In the case of low expression of the antigen at the cell surface, the primary and secondary antibody concentration can be increased, and in the case of transfected cells the experiment can be repeated using a higher amount of cDNA for transfection, so as to increase receptor surface expression.
2. In the case of insufficient amount of primary antibody, the latter can be increased up to 1 μg antibody /10^6 cells.
3. High background can be due to insufficient washing following incubation with antibodies, high concentration of primary or secondary antibody, or non-specific binding by the secondary antibody. The latter case can be addressed by using fluorescently coupled f(ab')$_2$ fragment of secondary antibody.

Background noise can also be reduced by incubating cells with 3% BSA or 5% normal goat serum prior to addition of primary antibody.

Some cells have high autofluorescence that may interfere with the specific signal. This can be addressed by looking at autofluorescence levels in cells not exposed to antibody treatment and adjusting the instrument settings so that the mean autofluorescent signal is between 0 and 10^1 (by consulting manufacturer's guidelines on altering instrument settings).

Immunofluorescence

Visualization of receptors on cells and tissues. This technique can be used to examine the subcellular localization of receptors in cells or tissue sections.

1. Cell lines: Poly-L-lysine coated coverslips (Fisher brand, Fisher Scientific, USA) are placed in 12 well plates (one/well). Cells (1 × 10^3) are plated on each well in complete media, and after 24 h the media are removed by suction, and the cells are washed twice with sterile PBS prior to fixation and immunofluorescence, as described below.
2. Tissue preparation: Sections from different regions of the brain are cut and placed into a small, soft-plastic, straight-sided ampoule (Fisher Scientific) with a push fit cap and enough saline (0.9%) to cover the tissue, and immersed in liquid nitrogen until frozen. Tissue samples are stored at –70ºC till use. The saline protects against tissue damage caused by the formation of ice crystals when the ampoule is transferred from –70ºC to –30ºC in the cryostat for sectioning. Cryostat sections (5–8 μm) are cut and transferred to microscope slides. The sections are allowed to air dry at room temperature for 2–24 h prior to fixation and immunofluorescence, as described below.

Cells/sections are fixed with 4% paraformaldehyde (pH 7.4) for 15 min at room temperature. Wells/slides are washed twice (5 min each) with Tris buffered saline (pH 7.4) and non-specific binding is blocked with 1% goat serum in TBS for 30 min. The cells/sections are incubated overnight at 4ºC with the appropriate primary antibody. The next day, wells/slides are washed four times (5 min each) with gentle shaking in TBS. Slides are incubated with the appropriate secondary antibody (rat or mouse FITC), for 60–90 min in the dark with gentle shaking. After incubation, the wells /slides are washed four times (5 min each) in TBS by gentle shaking. The cells/sections are sealed using Vector shield (Vector) and examined under a fluorescence microscope (Leica DM 6000B).

Problems and troubleshooting:

1. High background can be reduced by adding 0.1% Tween-20 to washes or increasing the concentration of normal serum (5–10%) used for blocking.
2. Some antibodies are sensitive to fixatives. In such cases, different fixatives (glutaraldehyde, methanol or 10% formalin) can be used.

Results and Discussion

In order to study the biochemical properties of endogenous opioid receptors, we generated antibodies to the N-terminal region of μ, δ, or κ receptors. The peptide sequences were chosen with the help of ExPASy software in order to avoid predicted N-glycosylation and phosphorylation sites. Monoclonal antibodies to μ (4D.6), δ (5A.2) and κ (7C.5) peptides were generated in mice, as described above. Here we present data using this synthetic peptide approach to antibody production. The N-terminal peptide sequences selected for the generation of antibodies to μ, δ or κ opioid receptors show a large diversity (least homology) among these receptors and can therefore be used in the generation of highly receptor specific antibodies. These peptides were synthesized on a poly-L-lysine backbone as MAPs leading to the formation of an immunogenic complex that does not require conjugation to a carrier molecule. This allowed the generation of antibodies to the peptide sequence of interest without the presence of contaminating anti-carrier antibodies. In addition, the presence of multiple copies of the desired antigenic sequence led to an increase in the immunogenic response of the animal.

We used the standard protocol described in the "**Generation of Antibodies—Monoclonal**" section to generate monoclonal antibodies to μ, δ or κ opioid receptors. Positive antibody-secreting clones were identified by antipeptide ELISA and subjected to subcloning by limiting dilution to ensure that the antibodies were produced by cells derived from a single clone. This is important, because the presence of non-secreting cells will over time lead to the loss of the antibody-secreting population, since they divide much more rapidly compared to antibody-secreting clones. We selected clones 4D.6 (μ-mAb), 5A.2 (δ-mAb) and 7C.5 (κ-mAb) for further studies, since they exhibited the highest titers in peptide ELISA. The antibodies were isotyped using an isotyping kit according to manufacturer's protocol (Sigma) and found to belong to the IgG2b subtype (Table). The antibodies showed receptor specificity at titers of 1: 750 (μ), 1: 800 (δ) and 1: 500 (κ) with an EC_{50} for the selective peptide ranging from 470–700 ng (Table). The antibodies were purified on protein-A Sepharose CL-4B column to characterize their receptor selectivity. For this, the opioid receptors cDNAs were transfected into HEK-293 cells, since the transient expression of opioid receptors in these cells leads to fairly high levels of expression, and the cells do not normally express opioid receptors (12). As controls we used untransfected HEK-293 cells. As seen in Fig. 1, the monoclonal antibodies show receptor subtype selectivity. When the cells are incubated with μ-mAb as a primary antibody, only μ-receptors are recognized and there is no significant cross-reactivity with δ or κ opioid receptors. Similarly, δ-mAb and κ-mAb recognize only δ or κ-receptors, respectively, and do not exhibit significant cross-reactivity with other opioid receptor subtypes.

Next we examined if the monoclonal antibodies could be used to immunoprecipitate opioid receptors from cells expressing the receptors. To permit visualization of the immunoprecipitated receptors, we used N-terminally Flag epitope tagged μ, δ or κ receptors transiently expressed in HEK-293 cells (and untransfected HEK-293 cells as a control). Cell lysates were immunoprecipitated using μ, δ or κ affinity purified monoclonal antibodies, as described in the "**Characterization of Antibodies—Immunoprecipitation and Western**

TABLE

Characterization of Monoclonal Antibodies to μ, δ and κ Opioid Receptors.

	Isotype[1]	Titer[2]	EC_{50}[3]
μ-mAb	IgG_{2b}	1: 750	703 ± 109
δ-mAb	IgG_{2b}	1: 800	485 ± 40
κ-mAb	IgG_{2b}	1: 500	467 ± 81

[1] Isotyping was carried out with an antibody isotyping kit according to manufacturer's (Sigma) protocol.

[2] Titer was determined by ELISA; wells were coated with 1 μg/mL of the antigenic peptide and secondary antibody dilution was 1:500.

[3] EC_{50} (effective concentration for 50% binding) in ng of MAP was determined using 1:100 dilution of the primary antibody and 1:500 dilution of the secondary antibody.

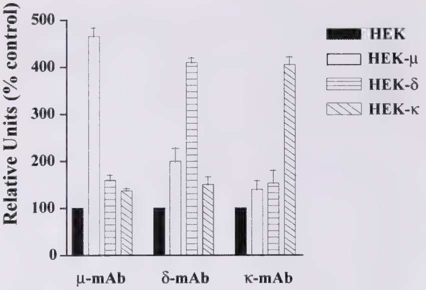

Fig. 1. HEK-293 cells transfected with either μ, δ or κ opioid receptors were used as antigens. ELISA was carried out as described in **Methods,** using either μ, δ or κ affinity purified mAb (1:1000 in PBS) as the primary antibody and HRP conjugated anti-mouse (1:1000 in PBS) as the secondary antibody. Untransfected HEK-293 cells were used as control and taken as 100%. Results are the Mean ± SEM (n=3) *p<0.001 represents significant differences from control.

Blotting" section. The immunoprecipitate was subjected to SDS-PAGE under reducing conditions and blotted with anti-Flag polyclonal antibody to visualize the receptors. We find that these antibodies are able to selectively immunoprecipitate the receptors. When cell lysates were subjected to immunoprecipitation with μ-mAb, we found a signal only in cells expressing μ but not δ or κ receptors. In the same manner, when cell lysates were immunoprecipitated with δ-mAb or κ-mAb, a signal was observed only from cells expressing δ or κ receptors but not from cells expressing other opioid receptors (Fig. 2). Since these antibodies are able to recognize endogenous receptors, we used the μ-mAb to immunoprecipitate μ-δ receptor complexes from mouse spinal cord tissue that is known to express μ, δ and κ receptors (15). We probed the immunocomplexes isolated using μ-mAb with commercially available polyclonal antibody against δ receptors (Chemicon International Inc., Temecula, CA). We found the presence of μ-δ complexes in tissues from wild-type animals but not δ k/o animals (15). Thus, these antibodies are useful for investigating opioid receptor heterodimers *in vivo*.

We also examined the ability of these antibodies to measure endogenous receptors by ELISA, using membranes from the various mouse brain regions. We found that the μ-Ab is able to recognize μ receptors in all regions but not in the cerebellum, consistent with the lack of significant μ receptors in this brain region. The data for midbrain and cerebellum are shown in Fig. 3. We confirmed this by using polyclonal antibodies raised in rabbit against 18-amino acids (381 – 398) of the μ opioid receptor (16) or to a 50-amino acid C-terminal polypeptide expressed as GST-C50 fusion protein (17). These antibodies have previously been shown to selectively recognize μ-receptors present in cell lines and tissues (18). Using an ELISA for membranes coated onto a 96 well plate, we have been able to develop a rapid screening assay that reliably measures the levels of μ-receptors in various regions of the brain. Thus, peptide selective antibodies to opioid receptors are useful in quantitating receptor levels in endogenous tissues.

In summary, we have shown that N-terminally directed antibodies generated against GPCRs are highly selective and can recognize recombinant as well as endogenous receptors. Our results suggest that this strategy of targeting the N-terminal region can be useful for the generation of antibodies to other members of the GPCR superfamily. These antibodies are powerful tools

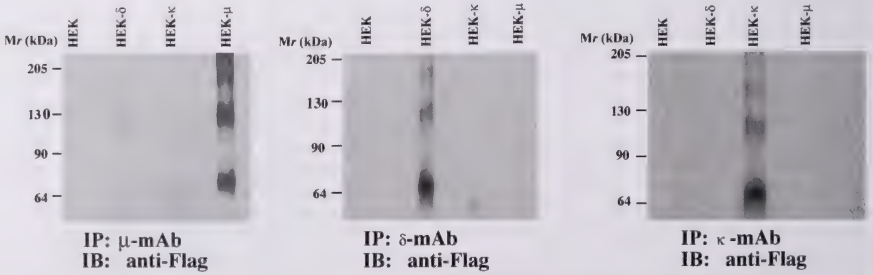

Fig. 2. HEK-293 cells transfected with either Flag tagged μ, δ or κ opioid receptors and untransfected HEK cells were solubilized with NP-40 lysis buffer and subjected to immunoprecipitation with 1 μg of either μ, δ or κ-mAb, as described in **Methods**. Immunoprecipitates were subjected to SDS-PAGE under reducing conditions and immunoprecipitated receptors identified by Western blot analysis using anti-Flag antibodies. A representative blot of three experiments is shown.

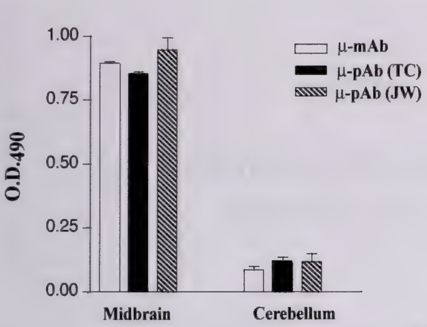

Fig. 3. Midbrain or cerebellar membranes (1 μg) were plated on 96 well plates and the level of μ receptors was detected by ELISA. Results are the Mean ± SEM (n=3). As a control against our antibodies (μ-mAb) we have used antibodies obtained from Tomas E. Cote (Bethesda, MD) and Jia-Bei Wang (Baltimore, MD). These are polyclonal antibodies generated against the C-terminal tail of μ opioid receptors.

for probing the biological function of GPCRs and could be of use in discovering new ligands and drugs, and in doing pharmacological research.

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Melvin D. Yahr Memorial Lecture

An Update on the Treatment of Parkinson's Disease

JOSEPH JANKOVIC, M.D.

Abstract

Although levodopa remains the most effective symptomatic drug for Parkinson's disease (PD), its use is limited by the emergence of motor fluctuations and dyskinesias, particularly in young-onset patients. Dopamine agonists, catechol-O-methyltransferase inhibitors and other anti-parkinsonian drugs have been found to diminish or prevent these complications and possibly to exert disease-modifying effects. The finding that the subthalamic nucleus (STN) and the globus pallidum internus (GPi) are abnormally active in PD has led to effective surgical treatments designed to improve patients' quality of life. The relative benefits of targeting STN or GPi with high-frequency stimulation are still being debated. Experimental therapeutics of PD include novel delivery systems, anti-apoptotic strategies and implantation of genetically engineered cells, and stem cells. Despite encouraging results from early pre-clinical and clinical studies, trials of human fetal grafts and intraventricular and intraparenchymal infusion of glial cell-line-derived neurotrophic factor have not shown clinically meaningful benefits. Future therapeutic strategies should focus not only on ameliorating the symptoms of PD, but also on neuroprotective or neurorescue therapies that can favorably modify the natural course of the disease and slow the progression of both motor and nonmotor manifestations of PD.

Key Words: Parkinson's disease, levodopa, dopamine agonists, dyskinesias.

Medical Treatment of Parkinson's Disease

THIS ARTICLE WILL FIRST SUMMARIZE current studies on medical approaches to treating Parkinson's disease (PD) and then present an update on neurosurgical treatments. Levodopa continues to be the most potent drug for controlling PD symptoms, particularly those related to bradykinesia, but the benefits may be outweighed by the emergence of motor complications, such as fluctuations and dyskinesias. To address the relative benefits and putative neurotoxicity of levodopa, a large multicenter study, the ELLDOPA (Earlier vs. Later LEVODOPA) trial, was designed to evaluate the effects of levodopa on the progression of PD (1). In this study, 361 patients never previously treated with nor requiring dopaminergic drugs were randomized to placebo or levodopa at 150, 300, or 600 mg/day for 40 weeks, followed by a 2-week washout. The total post-washout Unified Parkinson's Disease Rating Scale (UPDRS) score increased 7.8 points for placebo vs. 1.9 points for each of the two lowest doses and decreased 1.4 points for the highest dose ($p < 0.001$). Freezing was seen primarily in the placebo group, while wearing off and dyskinesias were more common in the highest-dose group (15 of 91 or 16.5% in the 600 mg group developed dyskinesia). A subset of patients (n=135) underwent single-photon emission tomography (SPECT) imaging using beta-CIT 2 beta-carbomethoxy-3 beta-(4-[(123)5]iodophenyl) tropane as a ligand for striatal dopamine transporter at baseline and at 9 months. No significant differences in loss of uptake were seen for any dose vs. those on placebo. However, when 21 of 142 scans without evidence of dopaminergic deficit (SWEDD) at baseline or at 9 months were excluded from the analysis, there was a significantly larger loss of uptake among all patients receiving levodopa and among high-dose patients vs. placebo. The decline of beta-CIT uptake in the striatum was significantly more pronounced in the levodopa groups than in the placebo group (–7.2%, –4%, –6%, and –1.4% in 600 mg/d, 300 mg/d, 150 mg/d, and placebo, respectively; p=0.04). Although

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Glossary

ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale
ADL = activities of daily living
AUC = area under the curve
CALM-PD = comparison of the agonist pramipexole with levodopa on motor complications of Parkinson's disease
CDS = continuous dopaminergic stimulation
CIT = carbomethoxy-3ss-(4-iodophenyl)nortropan
COMT = catechol-O-methyltransferase
DA = dopamine
DBS = deep brain stimulation
DOPA = dihydroxy-phenylalanine
ELLDOPA = Earlier vs. Later Levodopa
FDA = Food and Drug Administration
F-DOPA = 18F-Dopa or [^{18}F]fluorodopa
GABA = gama-aminobutyric acid
GDNF = glial cell-line-derived neurotrophic factor
GPe = globus pallidus externa
GPi = globus pallidus interna
Ki = influx rate constant
L-DOPA = levodopa
MAO-B = monoamine oxidase-type B
MMSE = Mini-Mental State Examination
MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NMDA = N-methyl-d-aspartate
PADRECS = Parkinson's Disease Research, Education, and Clinic Center
PD = Parkinson's disease
PET = positron emission tomography
SPECT = single photon emission tomography
STN = subthalamic nucleus
SWEDD = scans without evidence of dopaminergic deficit
TH = tyrosine hydroxylase
UPDRS = Unified Parkinson's Disease Rating Scale

the SPECT results are difficult to interpret, it is possible that they reflect a pharmacodynamic effect on the dopamine transporter rather than damaging effects on the dopaminergic neurons (2). There is a growing consensus among the experts that until the validity of the various neuroimaging studies in charting the course of the disease is well established, future clinical trials or neuroprotection should rely on clinical outcome measures (3, 4).

One of the most challenging problems in the management of PD is the treatment of levodopa motor and nonmotor complications (5). Although some studies have concluded that dyskinesias and motor fluctuations are rarely troublesome (6), other studies have shown that dyskinesias clearly have an adverse impact on a patient's quality of life (7). The "wearing off" effect, the most frequent form of motor fluctuation, appears to be related to the shortening of levodopa's half-life in the striatum as a result of the body's impaired capacity to store and buffer the striatal concentration of levodopa due to a loss of striatal dopaminergic terminals. This results in a more pulsatile, rather than continuous, delivery of levodopa, which has been postulated to lead to activation of post-synaptic signal transduction mechanisms, resulting in altered neuronal firing patterns in the globus pallidus interna—subthalamic nucleus—globus pallidus externa (GPe-STN-GPi) pathway, manifested clinically by motor fluctuations and dyskinesias (8).

The main strategies designed to decrease levodopa-induced dyskinesia include: (a) reducing each dosage of levodopa, (b) using drugs known to ameliorate dyskinesias, including amantadine, clozapine, and fipamezole, and (c) surgery. Continuous infusion is one strategy that has been shown to "smooth out" motor fluctuations (9, 10). In addition to adjusting levodopa dosing, reducing or stopping anticholinergic drugs may also ameliorate levodopa-related dyskinesias. Dystonia, whether levodopa-related or part of the disease (11), often improves with the administration of baclofen, anticholinergic drugs, dopamine (DA) agonists, lithium, and local injections of botulinum toxin (12).

Motor fluctuations, particularly the wearing-off effect, are usually best treated by reducing each individual dose and increasing the frequency of administration of levodopa, or by prolonging levodopa response with the addition of a DA agonist or inhibition of catechol-O-methyltransferase (COMT) by drugs such as entacapone (Comtan) and tolcapone (Tasmar). The latter COMT inhibitor is not frequently used, because of rare reports of liver toxicity. As a result of the 2006 Food and Drug Administration (FDA) ruling, the monitoring for possible liver toxicity of tolcapone has been relaxed, and the newly approved labeling states that serum liver enzymes should be tested at baseline as well as periodically (i.e., every 2–4 weeks) for the first six months of therapy. In addition, after the first six months of therapy, periodic monitoring is recommended at intervals deemed clinically relevant. Entacapone, because of its short half-life, requires frequent administration (200 mg, up to 8 times per day); most patients take entacapone with each dose of levodopa. COMT inhibitors may increase levodopa-induced dyskinesia, requiring a substantial (>25%) reduction in daily levodopa dosage. In 2003, the FDA approved triple combination tablets (Stalevo) containing carbidopa, levodopa, and entacapone in the following doses: 12.5/50/200, 25/100/200, and 37.5/150/200 for end-of-dose wearing off. In a randomized, crossover study of 132 healthy subjects, the levodopa area under the curve (AUC) was essentially the same in the triple combination as compared to separate administration, indicating equivalent pharmacokinetics (13). Whether initiating a COMT inhibitor at the time levodopa is started, rather than waiting until motor complications occur, will delay levodopa-related motor complications is still unknown, but the hypothesis is currently being studied in clinical trials, including the STRIDE-PD trial (14).

In contrast to the traditional DA agonists (bromocriptine and pergolide), pramipexole and ropinirole are non-ergolines and, therefore, are expected to have a lower risk of complications such as peptic ulcer disease, vasoconstrictive effects, erythromelalgia, pulmonary and retroperitoneal fibrosis, and cardiac valvular disease (15). A study of 301 patients in early stages of PD, followed in a double-blinded fashion for a mean of 2 years after randomization to pramipexole or levodopa (Comparison of the Agonist Pramipexole with Levodopa on Motor Complications of Parkinson's Disease or CALM-PD), found marked reduction in the risk of motor complications in the pramipexole group (16). A 4-year follow-up of the CALM-PD cohort found that: (a) initial treatment with pramipexole was associated with a significant reduction in the risk of developing dyskinesias (24.5% vs 54.0%, hazard ratio 0.37, $p < 0.0001$) and wearing off (47.0% vs 62.7%, hazard ratio 0.68, $p = 0.02$), but there was no difference between the two groups in disabling dyskinesias; (b) initial levodopa treatment resulted in a significant reduction in the risk of freezing (25.3% vs. 37.1%, hazard ratio 1.70, $p = 0.01$); (c) the improvement in mean total UPDRS was greater with levodopa than with pramipexole (2.0 ± 15.4 vs -3.2 ± 17.3 points, $p = 0.003$); (d) pramipexole treatment was associated with a higher risk of somnolence (36% vs 21%, $p = 0.005$) and edema (42% vs 15%, p 0.001); and (e) there was no difference in quality of life (17). Furthermore, sequential beta-CIT SPECT scans show that the rate of loss of dopamine transporter density as measured by the decline in beta-CIT over the 46-month period of follow-up was about 40% lower in the group initially treated with pramipexole (16.0%) as compared to the levodopa group (25.5%) (18). The difference in slopes, however, is significant only between baseline and 22 months, but not between 22 and 46 months. At 22 months patients treated with pramipexole and those on both pramipexole and levodopa had nearly identical (7%) declines in beta-CIT values from baseline as compared to 13.5% decline in patients treated with levodopa monotherapy. This suggests that the rate of loss of striatal beta-CIT may decrease as patients require more levodopa. This could be interpreted as indicating possible levodopa neurotoxicity, or that pramipexole and/or levodopa may have a direct effect on beta-CIT early in disease; there may be other reasons as well.

Ropinirole has also been demonstrated to be effective in early PD. In one study, 268 patients with early PD were randomized to either ropinirole ($n = 179$) or levodopa ($n = 89$) and followed for more than 5 years (19). After 5 years, approximately one half of the patients remained in the study (47% in the ropinirole group and 51% in the levodopa group) and 34% of those randomized to ropinirole remained on monotherapy (16.5 mg/day). The mean levodopa dose was 750 mg/day. Prior to the addition of levodopa, only 5% of the ropinirole-treated patients developed dyskinesia, in contrast to 36% of those treated with levodopa. After five years, only 20% of the patients on ropinirole or ropinirole/levodopa exhibited dyskinesias vs. 46% of those on levodopa. No significant differences were seen among groups for wearing off, freezing, or dopaminergic side effects, with the exception of hallucinations, which were more common in the ropinirole group. This study showed that the risk of developing dyskinesias was substantially lower with ropinirole monotherapy or with ropinirole plus levodopa supplementation. A follow-up study utilizing F-Dopa positron emission tomography (REAL-PET) showed a significantly slower decline in F-Dopa uptake in patients on ropinirole vs. levodopa. In this double-blind, European-Canadian, 2-year follow-up study, *de novo* patients not previously treated with dopaminergic drugs were randomized to ropinirole or Sinemet (20). The primary endpoint was a change in putamen 18F-Dopa uptake measured with 3-D positron emission tomography (PET), and secondary endpoints included incidence of dyskinesias. Of the 186 patients enrolled in the study, 21 were excluded because of normal 18F-Dopa PET. The mean dose at 2 years was 12.2 mg for ropinirole and 558 mg for levodopa. The 18F-Dopa uptake (Ki) in the putamen decreased an average of 13.4% in the ropinirole group ($n = 87$) and 20.3% in the levodopa group ($n = 75$), a 34% difference ($p = 0.022$). Using statistical parametric mapping analysis, the relative difference was 38% ($p < 0.025$). Although changes in the UPDRS motor score on medication favored the L-DOPA group by six points ($p = ns$) there was significantly less dyskinesia with ropinirole: 26.7% vs 3.4% ($p < 0.001$) and it took about 8 times longer for the ropinirole patients than the levodopa patients to develop dyskinesia ($p < 0.001$). Various statistical analyses of the PET data showed significantly slower (30–35%) loss of dopamine terminal function in early PD patients treated with ropinirole compared with levodopa. Both pramipexole and ropinirole (and possibly other DA agonists) have been associated with irresistible sleep attacks and excessive daytime drowsiness (21). This drowsiness can be at least partially reversed with modafinil (22).

Apomorphine is a water-soluble DA and, therefore, is suitable for intravenous, subcutaneous, sublingual, or intranasal administration. Subcutaneous injections or continuous infusions have been found to be useful even in advanced PD, by reducing the "off" time without necessarily increasing dyskinesias (23).

There are several new DA agonists being investigated in Phase 2 or 3 clinical trials. Rotigotine CDS (constant delivery system; SPM 962; N-0923), a new 5-hydroxy-2-aminotetralin derivative, is a highly selective D2 agonist, delivered through a silicone-based transdermal patch. It has been found to produce dose-related improvement in the UPDRS (24). Administration via a transdermal patch bypasses metabolism by liver, and as a result of sustained delivery more steady plasma and brain levels can be achieved. This may result in a smoother response and less severe motor complications. Another novel DA agonist is sarizotan (EMD128130; Merck KGaA), which, based on *in vitro* binding studies, has a high affinity for D2, D3, and in particularly D4 receptors, as well as 5-HT_{1A}. The drug has anti-psychotic effects and it reverses levodopa-induced dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys and other animal models of PD.

Psychiatric side effects of dopaminergic drugs, particularly agitation, visual hallucination, psychosis, paranoia, hypersexuality, and pathological gambling (25), may be controlled by reducing the dosage of these drugs (levodopa, dopamine agonists) and eliminating all other drugs that are not absolutely essential, such as selegiline, anticholinergics, and amantadine. Atypical antipsychotics offer the best strategy for controlling drug-induced psychosis without the need to adjust the dosage of dopaminergic drugs. Quetiapine fumarate (Seroquel), a dibenzothiazepine that blocks not only D1 and D2 receptors but also 5-HT_{1A} and 5-HT_2 receptors, has also been found to have a beneficial effect on PD patients with hallucinations. In contrast to olanzapine, quetiapine usually does not worsen parkinsonism. The role of ziprasidone (Geodon), a potent blocker of D2 and D3 receptors as well as 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1D} and α_1 receptors, and aripiprazole (Abilify), a partial D2 and 5-HT_{1A} agonist and 5-HT_2 antagonist, in the treatment of PD-related psychosis is still unknown. Cholinesterase inhibitors such as donepezil (26), rivastigmine, and galantamine, and the N-methyl-d-aspartate (NMDA) antagonist memantine, have been found to improve cognitive and language function in patients with PD. In a study of rivastigmine in dementia associated with PD, involving 541 patients enrolled in a 24-week, randomized, multicenter, double-blind clinical trial, the mean Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) score, the primary efficacy variable, improved by 2.1 points in the rivastigmine group and by 0.7 in the placebo group ($p < 0.001$), and the Mini-Mental State Examination (MMSE) improved by 0.8 in the rivastigmine group and worsened by 0.2 in the placebo group ($p = 0.03$) (27). At the end of the study, 55.5% of all patients were receiving 9–12 mg of rivastigmine per day.

There are no proven neuroprotective drugs (28), although selegiline, a monoamine oxidase-type B (MAO-B) inhibitor, has been found to delay the need for levodopa therapy and may reduce the risk of freezing (29, 30). In clinical studies, rasagiline, another MAO-B inhibitor, provides a modest benefit as an adjunctive therapy for PD patients experiencing levodopa-related motor fluctuations. Using a "randomized, delayed-start" design to distinguish between short-term and long-term effects of the medication, 371 patients were randomized to 1 or 2 mg/d of rasagiline for 1 year, or placebo for 6 months followed by rasagiline, 2 mg/d, for 6 months (31). The mean adjusted difference between placebo/rasagiline, 2 mg/d, vs. rasagiline, 1 mg/d, for 1 year was −1.82 UPDRS units ($p = 0.05$). The drug was very well tolerated, and subjects treated with rasagiline 1 and 2 mg/d for 1 yr showed less functional decline than subjects whose treatment was delayed for 6 months. A double-blind, placebo-controlled trial showed that after a 10-week treatment with rasagiline, 12 of 43 of patients (28%) had an improvement in total UPDRS score of 30% or greater, compared with none in the placebo group ($p < 0.05$) (32). In an 18-week, double-blind trial of 687 patients randomized to receive once-daily rasagiline (1.0 mg), entacapone (200 mg with each dose of levodopa), or placebo (the LARGO trial), both rasagiline and entacapone reduced "off" time by 1.2 hours as compared with placebo (0.4 hour reduction, $p \leq 0.0001$); the mean daily dose of levodopa was reduced by 24.3 mg/day on rasagiline and by 19.2 mg/day on entacapone, and was increased by 5.5 mg/day on placebo (33). Other variables showed that rasagiline was superior to placebo and to entacapone in reducing UPDRS motor score, and at least as effective as entacapone in reducing "off" time. In another study of patients with motor fluctuations, treatment with 1 or 0.5 mg/day of rasagiline was associated with a 29% (1.85 hour) and 23% (1.41 hour) reduction, respectively, in "off' time compared to baseline (34).*

One particularly promising therapeutic and potentially neuroprotective approach involves the use of neurotrophic factors, particularly the glial cell-line-derived neurotrophic factor (GDNF). This trophic factor has been reported to enhance the survival of midbrain dopaminergic neurons *in vitro* and to rescue degenerating neurons *in vivo* (35). The encouraging pre-clinical observations led to a pilot human, multicenter trial of intraventricular GDNF infusions in patients with moderately advanced PD. However, because of lack of observed efficacy and frequent occurrence of nausea, anorexia, tingling (Lhermitte sign), hallucinations, and depression, these trials were suspended (36). In a one-year follow-up of five patients with PD in whom GDNF was continuously infused directly into the putamen, there were no serious clinical side effects, a 39% improvement in the off-medication motor sub-score of the UPDRS, and a 61% improvement in the activities of daily living subscore. Furthermore, levodopa-induced dyskinesias were reduced by 64% and, in contrast to fetal implants (see below), there were no off dyskinesias (37). This clinical improvement was accompanied by a 28% increase in putamen PET F-DOPA uptake and evidence of neuronal sprouting in an autopsied brain (35). A recently completed multicenter trial, however, has shown no benefit from GDNF, and further studies have been suspended because of evidence of development of GDNF antibodies in some patients and cerebellar toxicity in experimental primates (38–40).

Other agents that are being or soon will be investigated as potential neuroprotective drugs include aspirin and salicylate, modafinil, minocycline (41), and even green tea, which contains polyphenol (-)-epigallocatechin-3-gallate (42) and has been reported to block the uptake of MPP+. Only well-designed clinical trials will be able to address the question of whether therapeutic interventions with these agents can favorably alter the natural course of the disease by promoting the survival and growth of degenerating neurons.

Another promising strategy in the treatment of PD is the use of adenosine antagonists. Adenosine A_{2A} receptors are colocalized with striatal dopamine D2 receptors on gamma-aminobutyric acid (GABA)ergic medium spiny neurons, which project via the "indirect" striatopallidal pathway to the GPe. In a 12-week, double-blind, randomized, placebo-controlled, exploratory study, PD subjects with both motor fluctuations and peak-dose dyskinesias were randomized to treatment with placebo ($n = 29$), istradefylline up to 20 mg/day ($n = 26$), or istradefylline up to 40 mg/day ($n = 28$) (43). There was no prespecified primary outcome measure, and 19 outcome variables were analyzed. As assessed by home diaries, subjects assigned to istradefylline experienced a mean (± SE) reduction in the proportion of awake time spent in the "off" state of $7.1 \pm 2.0\%$ compared with an increase of $2.2 \pm 2.7\%$ in the placebo group ($p = 0.008$). There was a decrease in "off" time of 1.2 ± 0.3 hours in the istradefylline group compared with an increase of 0.5 ± 0.5 hour in the placebo group ($p = 0.004$). Dyskinesia severity was unchanged, but "on" time with dyskinesia increased in the istradefylline group compared with the placebo group (percent, $p = 0.002$; hours, $p = 0.001$). No differences were observed in change in UPDRS scores or Clinical Global Impression of Change. Istradefylline was generally well tolerated, and it reduced "off" time, as assessed by home diaries. Severity of dyskinesia was unchanged, but "on" time with dyskinesia increased.

Neurosurgical Treatment of Parkinson's Disease

Deep Brain Stimulation

It is beyond the scope of this article to comprehensively review the neurosurgical treatment of PD. Only a brief review, focusing on high-frequency deep brain stimulation (DBS) will be provided here. Several studies have demonstrated that DBS of the GPi and STN improves parkinsonian symptoms and prolongs the "on" time. In a multicenter, prospective, double-blind, crossover study of 143 patients with advanced PD who received bilateral high-frequency stimulation of STN or GPi, the UPDRS motor scores improved by 49% ($p < 0.001$) and 37% ($p < 0.001$) respectively in comparison to the non-stimulated state (44). Furthermore, 6 months following implantation as compared to baseline, the percent time "on" without dyskinesias increased from 27 to 74 ($p < 0.001$) and 28 to 64 ($p < 0.001$) with STN and GPi DBS, respectively. Adverse events included intracranial hemorrhage in seven and lead explantation in two.

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*In 2006 rasagiline was approved by the FDA for initial monotherapy and as adjunct to levodopa.

While the levodopa dosage remained unchanged in the GPi group, the daily levodopa dose equivalents were reduced by 37% in the STN DBS group ($p < 0.001$). In a five-year prospective study of the first 49 patients, mean age 55 years, treated with bilateral STN DBS and assessed during "on" and "off" states at one, three and five year's, the Grenoble group found 54% improvement in "off" motor function as compared to baseline and 49% improvement in activities of daily living (ADL) (45). Speech was apparently the only motor function that did not improve. Except for improved dyskinesia and lower daily levodopa dose, there was no additional improvement in "on" motor function beyond one year, and the axial symptoms continued to deteriorate after the first year. Of the initial 49 patients, 7 did not complete the study, 3 died, 4 were lost to follow-up, 3 developed dementia after three years, one committed suicide and one had a large cerebral hemorrhage.

This and other studies provide evidence for the conclusion that STN DBS is no better than levodopa, but that it ameliorates levodopa-related motor complications and dyskinesias and off-period dystonia. Despite many reports concluding that GPi DBS is less effective than STN stimulation, there are only a few studies that have objectively compared these two approaches (46). Several studies have demonstrated greater anti-dyskinetic effects of GPi versus STN stimulation. Some studies have suggested that GPi DBS may be especially indicated in patients with a low threshold for dyskinesia (47), and GPi is considered the desirable target for treatment of dystonia and other hyperkinetic movement disorders. In their study involving 23 patients with PD complicated by marked levodopa-related motor fluctuations and dyskinesias, the investigators concluded that there were no significant differences in the overall benefits, although levodopa was decreased more in the STN group and dyskinesia improved more in the GPi group (48). Further controlled, randomized studies, however, are needed to determine which of the two methods is more effective and which patients should be considered the best candidates for either of the two procedures. Recently, the Veterans Administration initiated and sponsored a study designed to compare STN and GPi DBS in patients with PD as part of the Parkinson's Disease Research, Education, and Clinic Center (PADRECC) initiative. DBS of the STN has been found to be effective in controlling not only parkinsonian tremor (49), but also bradykinesia and handwriting, and possibly even gait difficulty and freezing (50).

Brain Grafting

Freed et al. (51) reported the results of the first double-blind, placebo-controlled trial of fetal graft transplantation for advanced PD. Forty patients, stratified by age into younger than and older than 60 years, with an approximately 7-year history of PD symptoms, were randomized to receive either 4 embryonic mesencephalons delivered via 4 needle passes to the left and right putamen or a sham operation (4 drill holes to the forehead without dural penetration). After one year, the "sham" patients were given the option to be implanted and were then followed in an open label manner; a total of 33 patients received an implant. Overall, there was no difference between the implanted vs sham patients with respect to the primary outcome variable, a global rating by the patients (from −3, PD markedly worse, to +3, PD markedly improved). However, 5 of 33 (15%) patients who eventually received the implant experienced dyskinesias even during "off" periods (presumably as a result of release of DA from the fetal implant), which were successfully treated with GPi DBS in 3 of the 5 patients (52). In the second, National Institutes of Health (NIH)-funded, controlled trial of fetal transplants, 34 patients were randomized to receive bilateral grafting into the posterior putamen of 4 or 1 fetal tissues per side, or sham surgery (partial burr hole without penetration of the dura) (53). All patients received immunosuppression for six months after surgery and were followed for 24 months. Thirty-one patients completed the trial; 2 died during the trial, and 3 afterward, for causes unrelated to the procedure. There was no significant overall treatment effect, but patients with milder symptoms did show significant improvement ($p = 0.006$). Post-mortem examination was performed on all patients who died; in all transplanted patients the tyrosine hydroxylase (TH) staining indicated striatal innervation, particularly in those who received 4 tissues. PET results indicated a significant dose-dependent increase vs. baseline in fluorodopa uptake, with no change in placebo patients and an approximate one-third increase in patients receiving 4 tissues. Despite these histochemical and imaging improvements, no significant differences were seen in clinical measures. Increase (worsening) from baseline in the UPDRS motor score while off medication was 9.4 for placebo, 3.5 for 1 tissue, and –0.72 for 4 tissues ($p=0.096$ for 4 vs. placebo). Although treated patients improved for approximately 9 months, they then worsened. There was no difference between implanted and sham patients in "on" time without dyskinesias, total "off" time, ADL scores, or levodopa dose required. No placebo patients, but 13 of 23 (56%) treated patients, developed off-medication dyskinesias. The authors concluded that "fetal nigral transplantation currently cannot be recommended as a therapy for PD based on these results."

In addition to human embryonic tissue, other donor sources are currently being investigated, including retinal pigment epithelial cells (Spheramine). These cells, located in the inner layer of the neural retina, produce dopamine. When attached to cross-linked gelatin microcarriers (Spheramine) and implanted stereotactically into the striatum, the cells have improved parkinsonian symptoms in rodents, non-human primates and parkinsonian patients. A pilot, open-label study of 6 patients showed 48% improvement in the UPDRS motor score 12 months after implantation (54). A randomized, controlled trial is currently being conducted in selected centers in North America and Europe.

Discussion

The most important principle in the management of PD is to individualize therapy and to customize it to the needs of the patients. The selected therapy should be based on scientific rationale and evidence-based data (55). It should be designed not only to control symptoms, but also to slow the progression of the disease and prevent levodopa-related complications. Since younger patients are likely to require dopaminergic therapy for a longer period of time and they are at increased risk for the development of levodopa complications, levodopa-sparing strategies such as the use of MAO inhibitors and dopamine agonists are even more critical for this population (56). Certain symptoms of PD, such as dysarthria, dysphagia, freezing and other "axial" symptoms, usually do not respond to dopaminergic therapy and may be mediated by non-dopaminergic systems (57). Patients whose functioning is impaired because of levodopa-related motor complications that cannot be controlled with medical therapy may be candidates for surgical intervention (58). As we achieve better understanding of the mechanisms of neurodegeneration, more effective therapeutic strategies will probably become available.

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Grand Rounds

The Role of High-Density Lipoprotein Cholesterol in Atherothrombosis

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Abstract

Despite considerable progress in the development of new therapies to control atherosclerosis and its complications, coronary heart disease (CHD) remains the number one cause of death in the Western world. While low high-density lipoprotein (HDL) has been associated with increased risk for CHD, raising HDL to reduce risk of disease has yet to be accepted as a standard therapeutic strategy. Currently available drugs that raise HDL (e.g., nicotinic acid, fibric acid derivatives, peroxisome proliferator-activated receptor agonists, and statins) also affect low-density lipoprotein (LDL) and other lipid constituents, making independent interpretation of their HDL-raising effect difficult to tease apart. Nevertheless, basic science studies suggest that HDL has multiple beneficial effects, and current efforts to develop new pharmacologic products with potent HDL-elevating effects may herald a day when HDL elevation becomes part of standard management of atherosclerotic diseases.

Key Words: High-density lipoprotein cholesterol, atherosclerosis, coronary heart disease, HDL elevating therapy, dyslipidemia, nicotinic acid, fibrate, statin, cholesterol ester transfer protein inhibitor, peroxisome proliferator-activated receptor ligands.

Introduction

The past half-century has seen tremendous progress in the fight against coronary heart disease (CHD). Modern medical therapy has resulted in a nearly 70% decrease in CHD-related deaths since 1950 (Fig. 1; 1). Yet despite this achievement, CHD remains the number one killer of Americans, with 1 in 5 Americans succumbing to this disease (2). With the aging of the American population, the socioeconomic impact of CHD will probably increase. While aging itself cannot be prevented, a lifestyle of healthy diet and exercise, and avoidance of tobacco products, can reduce one's risk level for the disease; appropriate pharmacologic therapy can also help. For example, cholesterol-lowering statins decrease cardiovascular events by 20–40%; they have become a routine part of CHD management. Fewer than half of all patients with

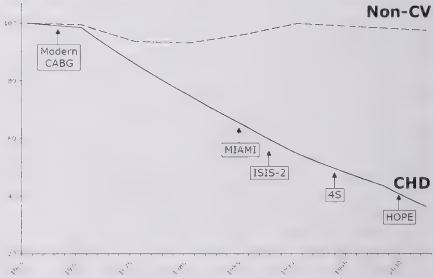

Fig. 1. Age-adjusted death rates in the United States secondary to coronary heart disease (CHD) and non-cardiovascular causes (Non-CV) by year, standardized to death rate in 1965 = 100 (1). This graph highlights some key clinical trials that may have played a role in the decline of CHD-related deaths, and future innovation will be needed to continue this progress.

CABG: coronary artery bypass graft; MIAMI: Metoprolol in Acute Myocardial Infarction; ISIS-2: Second International Study of Infarct Survival; 4S: Scandinavian Simvastatin Survival Study; HOPE: Heart Outcomes Prevention Evaluation.

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Glossary

ACS = acute coronary syndrome
apoA-I = apolipoprotein A-I
CETP = cholesterol ester transfer protein
CHD = coronary heart disease
CIMT = carotid intima-media thickness
DGAT2 = diacylglycerol acyltransferase 2
DM = diabetes mellitus
ETC-216 = apoA-I Milano
HDL = high-density lipoprotein
HPETE = hydroperoxyeicosatetraenoic acid
HPODE = hydroperoxyoctadecadienoic acid
HRT = hormone replacement therapy
IDL = intermediate-density lipoprotein
IVUS = intravascular ultrasound
LDL = low-density lipoprotein
LDLr = LDL receptors
LRPr = LDL-related protein receptors
PGI_2 = prostacyclin
PON = paraoxonase
PPAR-α = peroxisome proliferator-activated receptor-α
RCT = reverse cholesterol transport
SERM = selective estrogen receptor modulator
TFPI = tissue factor pathway inhibitor
TG = triglycerides
TIA = transient ischemic attack
TNF = tumor necrosis factor
TZD = thiazolidinedione
VLDL = very-low-density lipoprotein

symptomatic CHD were receiving lipid-lowering therapy in 2001 (2), but less than three years later, a national registry of patients admitted for CHD-related problems revealed that 88% received a cholesterol-lowering agent as one of their discharge medications (3). With all this progress, it remains somewhat frustrating that CHD is still the number one cause of death; therefore, considerable research is being undertaken to develop new pharmacologic strategies to further combat this epidemic. While statins have become a mainstay of modern CHD therapy, they primarily address one component of the lipid profile: low-density lipoprotein (LDL), the "bad cholesterol." As LDL is aggressively lowered, progression of atherosclerosis slows and patients with CHD have fewer deaths and heart attacks (4, 5). If LDL levels are optimized by aggressive use of statins, additional lowering may not result in meaningful additional benefit; therefore, raising high-density lipoprotein (HDL) has attracted attention as a potential therapeutic adjunct to statin therapy.

HDL is popularly known as the "good cholesterol." Population studies have demonstrated that as HDL levels increase, the incidence of CHD decreases. An analysis of four epidemiologic studies conducted in the United States suggested a 2–3% decrease in CHD risk for each 1% increase in HDL (6). The inverse relationship between HDL and CHD invites speculation that raising HDL may be an ideal therapeutic goal, to help decrease CHD. Furthermore, low HDL levels are very common among Americans, and 26.4% of those over 20 years old (39% of men and 15% of women) have low HDL (defined as HDL less than 40 mg/dL) (2, 7). Guidelines adopted by the American Heart Association, however, stop short of recommending HDL elevation as a specific therapeutic goal, primarily for three reasons (8). First, correlation does not imply causation; low HDL level and CHD may be related, but some other factor that affects both HDL and CHD may be the true culprit. Second, currently available therapies that have an HDL-raising effect also affect atherogenic lipoproteins such as LDL, so the effect that can be attributed solely to the HDL increase is difficult to tease out (Table 1; 8–10). Third, lifestyle changes such as taking up exercise and quitting smoking also raise HDL, and these interventions come without pharmacologic side effects. Nonetheless, with 20% of American deaths from CHD, new interventions are necessary, and research continues to accumulate supporting HDL elevation as a potential target. In this review, we explore the rationale behind this strategy.

The Role of HDL in Lipid Metabolism

Cholesterol in the body is composed chiefly of LDL ("bad") and HDL ("good"). LDL deposits lipids in the arterial wall, making the artery narrower, but HDL transports the lipids back to the liver. This balance between LDL and HDL is critical to the rate of formation of atherosclerotic lesions. If the proportion of LDL to HDL is raised, then more lipids will be deposited in arterial walls, leading to greater CHD, but if the ratio of HDL to LDL is elevated, then atherosclerotic lesions may regress, contributing to a reduction in heart attacks (Fig. 2).

Understanding this balance between LDL and HDL allows one to see the promise of HDL-elevating therapy. Designing therapeutic strategies, however, requires a greater understanding of how **reverse cholesterol transport** works. HDL plays a central role in lipoprotein metabolism (Fig. 3). The

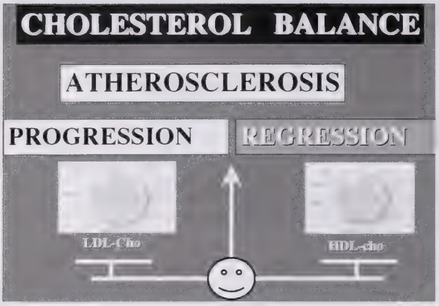

Fig. 2. The balance of LDL to HDL tips the scale toward atherosclerotic progression if there is more LDL or toward regression if there is more HDL.

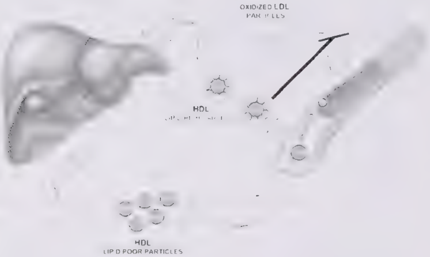

Fig. 3. The role of HDL in lipoprotein metabolism. HDL may prevent atherosclerotic development by engaging in reverse cholesterol transport from the arterial wall to the liver as well as blocking oxidized LDL particles from accumulating in the artery.

liver secretes apolipoprotein A-I (apoA-I), which acts like an empty vessel to accumulate lipids. Once the apoA-I has absorbed lipids from the arterial wall, it becomes HDL. HDL may accept additional free cholesterol from the vessel wall via another pathway on vessel wall macrophages (11). The lipid-laden HDL may then transport the removed cholesterol to the liver for disposal. This process, termed "reverse cholesterol transport" (RCT), is the principal mechanism behind the hypothesized benefit of HDL elevation. Much recent attention has focused upon a second HDL-based RCT mechanism. Cholesterol within HDL is transferred to LDL by a protein called "cholesterol ester transfer protein" (CETP), and this LDL may be returned to the liver by LDL receptors (LDLr) and LDL-related protein receptors (LRPr) (12). HDL also prevents arterial wall macrophages from absorbing oxidized LDL by hydrolyzing it (13). The final mechanism by which HDL may prevent atherosclerosis is by decreasing the number of endothelial cell adhesion molecules, which serve as an entry point for monocytes into the arterial wall (14).

Understanding the biology of HDL allows us to speculate upon the effects of potential therapeutic targets on its metabolic pathway. Increasing apoA-I or decreasing CETP, for example, would probably increase the quantity of HDL; however, RCT may not necessarily increase in both situations—if the elevation in HDL is limited to lipid-laden HDL without hepatic uptake, then HDL elevation alone may falsely indicate clinical benefit. If HDL elevation, however, successfully results in reduction in lipid content within the vascular wall, then the atherosclerotic lesion may resemble a more stable plaque that is lipid-poor and with a thicker fibrous cap rather than a lipid-rich plaque with a thin fibrous cap, which is more vulnerable to rupture that can cause myocardial infarctions (15).

Other Protective Effects of HDL

HDL has other effects beyond RCT that reduce atherosclerosis. The antioxidant, anti-inflammatory, endothelial function enhancement, and antithrombotic properties of HDL suggest a beneficial effect independent of RCT (Fig. 4).

Antioxidant Effects

Oxidized LDL attracts monocytes, and when monocytes consume oxidized LDL, they become foam cells. Foam cells cause platelets to become more active, smooth muscle cells to proliferate and thicken the arterial wall, and arteries to constrict by decreasing nitric oxide, a potent vasodilator (16). As an antioxidant, HDL can inhibit the oxidation of LDL, thereby preventing these steps

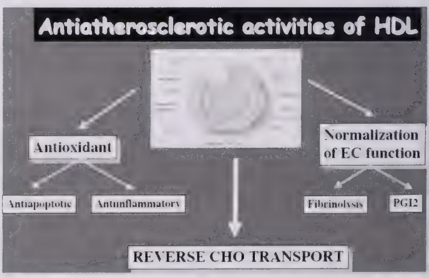

Fig. 4. Atheroprotective features of HDL include effects beyond reverse cholesterol transport.

from occurring. The reason for HDL's antioxidant effect may simply be its high antioxidant content, but HDL also contains several enzymes which directly prevent LDL oxidation. HDL transports an enzyme called paraoxonase (PON), which catalyzes the degradation of oxidized LDL phospholipids (17). If these oxidized phospholipids were not degraded, they could stimulate an inflammatory response and subsequent monocyte adhesion to the endothelium, accelerating atherosclerosis (18). The importance of PON's antioxidant effect has been further demonstrated in animal studies. In the absence of PON activity, HDL loses its atheroprotective effect in a mouse model (19), but increased expression of apoA-I increases PON activity (20). Furthermore, genetically modified animals that do not have PON are more susceptible to atherosclerosis (21), but those that overexpress PON have less atherosclerosis (22). Population studies of humans confirm the benefit of PON. Patients with more PON have fewer heart attacks (23), and low PON activity in a cohort of adult men was associated with more heart attacks (24). ApoA-I itself may also exert an anti-oxidant effect by reducing the "seeding molecules" hydroperoxyeicosatetraenoic acid (HPETE) and hydroperoxyoctadecadienoic acid (HPODE), which induce the oxidation of lipoprotein phospholipids (25).

Anti-inflammatory Effects

Experimental evidence suggests that HDL may be directly anti-inflammatory. HDL inhibits an enzyme called sphingosine kinase in endothelial cells; this action decreases sphingosine 1-phosphate, a key molecule in mediating inflammatory processes also mediated by tumor necrosis factor (TNF) (26). In a pig model, HDL inhibited expression of IL-1α-induced E-selectin, another marker of inflammation, by endothelial cells *in vivo* and *ex vivo*, further suggesting anti-inflammatory benefit (27).

Endothelial Function

Atherogenesis starts with a dysfunctional endothelium (28). Endothelial dysfunction initiates a cascade of events leading to blood that more easily clots, loss of nitric oxide, which causes blood vessels to constrict, and leukocyte adhesion and migration, which accelerates atherosclerotic plaque formation (Fig. 5; 29); but HDL improves endothelial function. Endothelial cells exposed to HDL decrease adhesion molecule expression, which prevents macrophage accumulation within the arterial wall (30). Also, in hypercholesterolemic men with endothelial dysfunction and low HDL, infusion of HDL restored endothelial function by restoring NO bioavailability (31, 32). Also, HDL may exert an anti-apoptotic effect upon vascular endothelial cells, which prevents these cells from self-destructing (33). The prevention of apoptosis may make a plaque less vulnerable to rupture. Therefore, HDL may help across the spectrum of atherosclerotic disease by preventing initiation of atherogenesis by improving endothelial function, and additionally decreasing atherosclerotic burden and increasing plaque stability for patients with advanced disease.

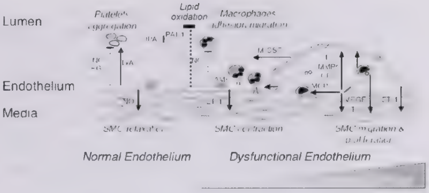

Fig. 5. Endothelial dysfunction initiates atherogenesis. Dysfunctional endothelium facilitates atherosclerosis development via impaired endothelium-dependent vasodilation, upregulated platelet aggregation and thrombogenicity, increased macrophage adhesion and migration and SMC proliferation (29).

CAM: cell adhesion molecule; CRP: C-reactive protein; ET: endothelin; MCP: monocyte chemotactic protein; M-CSF: monocyte colony stimulating factor; MMP: matrix metalloproteinase; NO: nitric oxide; PAI: plasminogen activator inhibitor; PGI2: prostacyclin; SMC: smooth muscle cell; TF: tissue factor; tPA: tissue type plasminogen activator; TxA2: thromboxane A2; VEGF: vascular endothelial growth factor.

Anti-thrombotic Effects

When atherosclerotic plaques rupture, thrombus formation occurs—it is this thrombus that can have devastating consequences if it completely occludes the vessel. Experimental evidence suggests that HDL is also anti-thrombotic, which may help to prevent this type of vessel closure, and the myocardial infarctions that result. In a study of hypercholesterolemic men, serum HDL level was a significant independent predictor of platelet thrombus formation within the Badimon perfusion chamber (34). Also, addition of apoA-I inhibited arterial thrombus formation in a mouse model (35). In an *in vitro* study, HDL enhanced inactivation of coagulation factor Va, thereby reducing thrombogenicity (36). In another *in vitro* model, the protein components of HDL, specifically apoA-I and apoA-II, were found to activate fibrinolysis, which is the process by which thrombi are broken down (37). HDL would, therefore, shift the hemostatic balance to fibrinolysis over thrombosis, which is favorable to the patient vulnerable to acute coronary syndrome (ACS). Tissue factor potently increases thrombogenicity, and HDL also has been shown to contain a tissue factor pathway inhibitor (TFPI) (38). HDL and apoA-I have also been shown to decrease the procoagulant activity of red blood cells (39). Oxidized LDL is particularly thrombogenic (40), and by reducing LDL, HDL would be additionally anti-thrombotic. HDL also stabilizes prostacyclin (PGI_2), which prevents thrombus formation between platelets and the vessel wall (41). Therefore, the current evidence suggests an overall anti-thrombotic effect of HDL.

Pre-clinical Evidence for the Effects of HDL Elevation

Teasing apart the effects of HDL in clinical trials has been difficult, as the medications used to study the effect of HDL elevation affect the parameters of other lipids as well (e.g., LDL, triglycerides [TG], etc.). The direct effect of HDL, however, has been demonstrated in animal models. In the seminal work on HDL infusion by Badimon et al. (42), HDL infusion into rabbits fed with a high-cholesterol diet resulted in decreased progression and regression of established atherosclerotic lesions and aortic lipid content. In another study, plaque regression, as measured by intravascular ultrasound (IVUS), was seen after direct infusion of apoA-I Milano into hypercholesterolemic rabbits within 72 hours, suggesting that reverse cholesterol transport is extremely rapid with this drug (43). Interestingly, apoA-I Milano infusion was also shown to reduce in-stent restenosis in a pig coronary artery model, suggesting that the effect of apoA-I Milano may extend beyond just RCT and include reduction of this complication of stent placement (44).

Current Treatment Options for HDL Elevation

Table 1 lists cardiovascular drugs that are known to raise HDL. However, their multiple effects upon other lipid parameters, as mentioned above, limit our ability to understand their effect on HDL independent of their effect on LDL and TG.

TABLE 1

Effect of Lipid-Lowering Drugs on Lipid Profile

	HDL	LDL	TG
Nicotinic acid	+15 to +35%	−5 to −25%	−20 to −50%
Fibric-acid derivatives	+10 to +35%	−5 to −20%	−20 to −50%
Statins	+5 to +15%	−18 to −55%	−7 to −30%
Thiazolidinediones	+5 to +13%	−4 to +16%	−26 to +2%
Bile acid sequestrants	+3 to +5%	−15 to −30%	−1 to +1%
Ezetimibe	+1 to +5%	−18 to −20%	−5 to -11%

The effects of currently available pharmacologic agents upon the lipid profile (8 – 10). Drugs that raise HDL affect other lipid parameters, increasing the difficulty of determining the effect on CHD attributable to HDL elevation alone.

HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides.

Niacin

Niacin is a B complex vitamin used for the treatment of high cholesterol since the 1950s. Niacin makes apoA-I last longer in the body, facilitating greater RCT by making apoA-I more available (45). Niacin also inhibits an enzyme, hepatic diacylglycerol acyltransferase 2 (DGAT2), which helps to make triglycerides destined for very-low-density lipoprotein (VLDL) (46). These effects of niacin cause an increase in HDL and decrease in LDL and TG, changes which have been demonstrated to reduce the complications of atherosclerotic disease.

In the Coronary Drug Project (CDP), a randomized, double-blind, placebo-controlled trial involving 8,341 men with prior myocardial infarction, which was started in 1966 (47), patients taking niacin had significantly fewer cardiovascular events and lived longer than those who received placebo (48). Niacin therapy, however, may be difficult for patients to tolerate, since it can cause flushing of the skin. Some 85% of patients taking immediate-release niacin experience flushing (49); in fact, 75% of patients in the niacin arm of the CDP dropped out of the study, mostly because of flushing (50). Slow-release niacins have reduced this side effect and have made this class of drugs more tolerable—only a quarter of patients taking the slower-release niacins experience flushing (49). Still, for those patients experiencing the problem, adhering to this regimen can be difficult. Niacin has also been criticized for making control of glucose more difficult (51); however, the CDP data suggest that this effect upon control of blood sugar does not significantly impact upon patients (48).

Fibric Acid Derivatives

Fibrate binding to peroxisome proliferator-activated receptor-α (PPAR-α) receptors causes an upregulation of a cascade of genes involved in endothelial function and RCT (29). The only fibrates currently approved for use in the U.S. are fenofibrate and gemfibrozil, but other fibrates used in other countries include bezafibrate, ciprofibrate and clofibrate. Fenofibrate also prolongs the lifespan of apoA-I, and it promotes the breakdown of VLDL, intermediate-density lipoprotein (IDL), and LDL (52). Ciprofibrate stimulates the arterial wall to give up its lipid content to HDL (53). Similar to niacin, gemfibrozil has also been shown to decrease synthesis of triglycerides and decrease apoB secretion (54). The net effect upon the lipid profile is similar to that found with niacin—decreased TG and LDL, increased HDL.

The largest trials of fibric acid derivatives in CHD patients are the CDP, which had 2,248 men with CHD on clofibrate (50); the Bezafibrate Infarction Prevention trial (BIP) with 3,090 adults with CHD on bezafibrate (55); the Helsinki Heart Study (HHS) with 4,081 hypercholesterolemic men on gemfibrozil (56); and the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) with 2,531 men with low HDL and CHD on gemfibrozil (57). While the CDP and BIP trials showed no benefit with fibrate (50, 55), the other trials did. HHS showed a one-third decrease in the incidence of CHD (56), and the VA-HIT demonstrated a 22% reduction in non-fatal myocardial infarction or death from coronary causes (57). Attributing the benefit exclusively or primarily to HDL elevation remains difficult; in the VA-HIT, for example, HDL increased by only 6%, but TG decreased by 31%. Therefore, these trials need to be carefully interpreted before one can reach a firm conclusion about the relationship between HDL and cardiovascular risk reduction.

Statins

The benefit attributable to HDL elevation is even more difficult to determine in statin trials. Statins have great ability to reduce LDL, but only limited ability to raise HDL. Furthermore, the effect on HDL differs depending on the statin, and higher doses do not necessarily translate into higher HDL. For example, in the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial, the percent increase in HDL decreased as the dose of atorvastatin (the most commonly prescribed statin in the United States) doubled (Table 2; 58). In an analysis that pooled data from 19 statin trials to examine the link between HDL and CHD, an effect of HDL on morbidity and mortality could not be determined, as the HDL effects in many of these trials were minimal (59). Nevertheless, because of their potent LDL-lowering effect, statins are the first-line treatment for dyslipidemia and for primary and secondary prevention of CHD.

TABLE 2
Change in HDL by Atorvastatin Dose

Atorvastatin Dose	HDL Increase (mg/dL ± SEM)
10 mg	2.9 ± 0.05
20 mg	2.4 ± 0.05
40 mg	2.2 ± 0.04
80 mg	1.1 ± 0.02

HDL level by atorvastatin dose in the STELLAR trial (error bars represent standard error) (58). As the dose of atorvastatin doubles, the effect upon HDL elevation declines, and the change across all doses is modest. Statins exert their effect primarily upon LDL and are not good monotherapy choices for HDL elevation alone.

SEM: standard error of the mean.

Thiazolidinediones

Thiazolidinediones (TZDs) are PPAR-γ agonists (29). TZDs make the body more sensitive to insulin, so they are primarily used to control blood sugar in Type II diabetes mellitus (DM), which makes their use particularly beneficial in addition to statin therapy for lipid management of the diabetic patient. The two TZDs approved for use in the United States—pioglitazone and rosiglitazone—affect lipids differently. While both raise HDL, pioglitazone lowers TG and has little or no effect upon LDL, whereas rosiglitazone raises LDL and has minimal effect upon TG (Fig. 6; 60). However, despite raising LDL, rosiglitazone decreased in-stent restenosis by 74% in a study of diabetic patients undergoing coronary intervention (61). Also, pioglitazone in a diabetic population and rosiglitazone in a non-diabetic CHD group were associated with decreased progression of carotid intima-media thickness (CIMT), which is correlated with decreased CHD (62, 63). However, no trial to date has demonstrated an impact of TZDs on hard endpoints such as mortality, and as with niacin and the fibrates, the TZDs' multiple other effects on hyperglycemia and LDL make it difficult to separate out their specific effect upon HDL elevation.

Bile Acid Sequestrants

Cholestyramine, colesevelam, and colestipol are bile acid sequestrants which block the absorption of bile from the gut to prevent this substrate of hepatic production of cholesterol from reaching the liver, so intestinal production of apoA-I is increased (64). In the Lipid Research Clinics Coronary Primary Prevention Trial, a study of 3,806 hypercholesterolemic men without CHD had a 19%

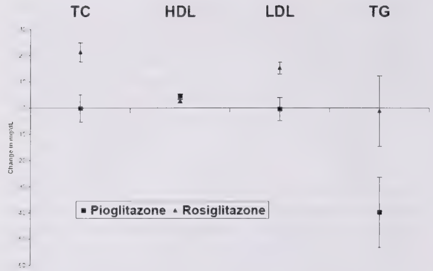

Fig. 6. Comparative effects of pioglitazone and rosiglitazone upon lipid parameters (error bars represent 95% confidence intervals) (60). Although both TZDs raise HDL and both have shown positive effects upon secondary endpoints of atherosclerotic disease, they have significantly different impacts upon LDL and TG. The clinical consequences of these differences have yet to be definitively determined by morbidity or mortality data from randomized controlled clinical trials.

TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides.

reduction in the incidence of CHD with cholestyramine (65). But these drugs can be difficult to tolerate, as gastrointestinal side effects, especially constipation, are common. Their effect upon HDL elevation, though, is negligible compared to their effect upon LDL (Table 1), so the benefits seen with these drugs are more likely due to their effect upon LDL.

Ezetimibe

Similar to the bile acid sequestrants, ezetimibe prevents intestinal cholesterol absorption, but by a different mechanism. Ezetimibe promotes efflux of dietary cholesterol and plant sterols from the intestinal wall back into the lumen, thereby decreasing cholesterol absorption (66). The effects upon HDL are modest and probably outweighed by the effect upon LDL, but it is interesting that ezetimibe also reduces atherosclerosis in animal models (67). Benefit in humans has not been conclusively demonstrated by reduction in morbidity or mortality, but for patients with difficulty controlling cholesterol with statins alone, this drug is a welcome addition.

Combination Therapy

By combining the above drugs, an additive effect upon HDL elevation has been achieved, with possible benefit. The Armed Forces Regression Study (AFREGS) examined 143 military retirees with low HDL and CHD and found that the combination of gemfibrozil, niacin and cholestyramine increased HDL by 36%, decreased angiographic stenosis of the coronary arteries by 0.8%, and decreased cardiovascular events (death, hospitalization, cerebrovascular event or transient ischemic attach [TIA], revascularization) (68). The regression seen in coronary blockages is suggestive of RCT. The HDL-Atherosclerosis Treatment Study (HATS), another trial of patients with low HDL and CHD, found that for patients on statin-niacin combination therapy, HDL increased 26% and LDL decreased 42%, with a significant 0.4% regression of angiographic coronary stenosis and 60% reduction in major adverse cardiovascular events (69). Unfortunately this study did not compare statin-niacin to niacin or statin monotherapy, which confounds the ability to isolate the incremental benefit of niacin. However, the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER)-2 study evaluated the impact of providing niacin to statin-treated patients with known CHD and moderately low levels of HDL on carotid atherosclerosis progression. The study found that the addition of niacin to statins limited atherosclerotic progression, but those on statin monotherapy increased their carotid atherosclerosis by a significant 5% (70). AFREGS, ARBITER-2 and HATS collectively suggest that HDL elevation may either stem progression or even induce regression of atherosclerotic burden.

Currently Available Alternative Treatment Options for HDL Elevation

Table 3 (71–76) lists treatments that raise HDL, but have unknown or mixed clinical benefit. Phenytoin, an antiseizure drug, raises HDL by an unknown mechanism. Observational studies suggest a cardiovascular benefit (79), and in a mouse model phenytoin reduced aortic atherosclerosis (80). However, conclusive randomized control trials have not been conducted, as the side effects of this medication—including psychomotor retardation, gingival hyperplasia, osteomalacia and coarse facies—and multiple drug-drug interactions limit the serious consideration of phenytoin as a lipid-modifying agent.

Some have speculated that the decrease in CHD among consumers of moderate amounts of alcohol, especially red wine, derived from alcohol's ability to raise HDL. It is true that alcohol elevates HDL by increasing the availability of apoA-I (81), and alcohol stimulates cellular cholesterol efflux, an early step of RCT (82). However, the American Heart Association does not recommend alcohol con-

TABLE 3
Alternative HDL-Elevating Drugs

	Change in HDL
SERM	−2 to +14%
HRT	+7 to +13%
Phenytoin	+10 to +13%
EtOH	+7 to +12%

Alternative interventions to raise HDL (71–76). These interventions have been demonstrated to raise HDL, but the clinical relevance is mixed. In the case of SERMs, some may provide cardiovascular benefit, but definitive randomized clinical trials are not yet completed. HRT, though previously assumed to be cardioprotective, has now fallen out of favor with the results of the Women's Health Initiative (WHI) study (77, 78). Phenytoin and alcohol consumption are of possible benefit but come with multiple adverse effects that limit their clinical potential in this regard.

SERM: selective estrogen receptor modulator; HRT: hormone replacement therapy; EtOH: ethanol.

sumption for cardiovascular reasons, counseling that "alcohol use should be an item of discussion between physician and patient (83)." Alcohol can also cause a host of other medical and psychological problems, so any gain for the heart has to be weighed against many other potential complications.

While National Cholesterol Education Program Adult Treatment Panel II (NCEP ATP II) advised that hormone replacement theory (HRT) should be considered as a treatment option for the prevention of cardiovascular disease in postmenopausal women (84), this theory has since been soundly disproven. It had been speculated that since HRT raises HDL and decreases LDL, it might be cardioprotective. However, multiple clinical trials have demonstrated that HRT actually increases cardiovascular complications (85, 86), and now HRT is no longer recommended for cardiovascular risk reduction (8).

Selective estrogen receptor modulators (SERM) also raise HDL (Table 3), and animal studies, clinical trial data, and population-based studies suggest a possible benefit (86–88). However, the effects of different SERMs vary—tamoxifen and raloxifene minimally change total HDL and increase certain HDL subfractions whereas toremifene increases total HDL (71, 89). SERMs seem to inhibit cholesterol synthesis (90). While SERMs are not currently used for the treatment of cardiovascular disease, since no trial was conducted specifically for that purpose, the Raloxifene Use for the Heart (RUTH) trial is currently underway. RUTH has enrolled 10,101 postmenopausal women with heart disease or at high risk for CHD to see if raloxifene reduces these women's CHD risk (91).

Emerging Approaches for HDL Elevation

The promise of HDL elevation as a means to further reduce the risk of CHD has attracted considerable interest, and investigations with this aim are currently underway. The drugs in most advanced development are the CETP inhibitors and apoA-I Milano.

Cholesterol Ester Transfer Protein (CETP) Inhibition

Patients with inherited CETP deficiency have elevated HDL. Homozygotes for CETP deficiency have six times the incidence of elevated HDL, and heterozygotes have twice the HDL levels of nonmutants (92). While this mutation is particularly prevalent in the Japanese population (93), and the native Japanese have the longest lifespan as a population in the world, CETP deficiency may not necessarily result in reduced CHD. In a population study of Omagiri City, Akita Prefecture in Japan, where CETP deficiency occurs 20 times more frequently than in the general population, HDL above 70 mg/dL was associated with increased CHD (94). This study also found that those over 80 years of age were less likely to have the CETP mutation, and CETP deficiency was associated with increased CHD (94). Elevated HDL secondary to CETP deficiency, therefore, may not be entirely atheroprotective. If CETP inhibition results in accumulation of lipid-laden HDL but not lipid-deficient HDL, there would be less lipid-deficient HDL to participate in RCT. On the other hand, animal models suggest that partial inhibition of CETP reduces atherosclerosis. Whether by oral small molecule (95), via vaccine-induced antibodies to CETP (96), or via anti-sense nucleotides against CETP (97), CETP inhibition resulted in reduction of atherosclerosis in rabbit models. Impressive increases in HDL have been seen in human studies of CETP inhibitors. Torcetrapib, a small molecule inhibitor of CETP, increased HDL by 46–106% (98), and JTT-705, another small molecule CETP inhibitor currently in development, increased HDL by 34% and modestly reduced LDL by 7% (99). Definitive clinical trials are underway.

apoA-I Milano

Another genetic mutation led to the development of another drug known as apoA-I Milano or ETC-216. In the village of Limone sul Garda in Italy, there are approximately 40 persons who have very low HDL (10–30 mg/dL) but nevertheless have longer life spans than normal (100, 101). They have a mutant type of apoA-I which is now known as apoA-I Milano. Infusions of ETC-216 reduced in-stent restenosis in a pig model (44), reduced lipid content of atheromatous plaques and macrophages in a mouse model (102), and protected the *in vivo* rabbit heart from regional ischemia-reperfusion injury (103), suggesting that apoA-I Milano, as a lipid-deficient apolipoprotein, may reduce atherosclerosis by scavenging lipid from the arterial wall in RCT and by other beneficial non-RCT related effects. Weekly ETC-216 infusion in patients with acute coronary syndrome resulted in a 1.1% regression of atherosclerotic lesions after only 5 treatments, suggesting rapid RCT (104). Whether this regression will translate into reduced cardiovascular events or paradoxically increase events through plaque destabilization remains to be discovered through additional clinical trials. A limitation of apoA-I mimetics, though, is that they must be administered parenterally because gastrointestinal proteases prevent effective oral use. IV administration would limit the potential settings in which these drugs may be used, but inpatient use or administration based upon a "chemotherapy"-type outpatient model may be successful in patients with severe atherosclerotic burden.

Conclusion

The rationale for HDL elevation as a therapy for CHD appears scientifically sound and the therapy may provide a much-needed addition to the pharmacologic armamentarium. HDL plays a central role in RCT and also has antioxidant, anti-inflammatory, anti-thrombotic and endothelial-function-promoting characteristics. Via its RCT mechanism, HDL holds the promise of not only halting progression of atherosclerosis but also inducing a true regression of lesions. A number of HDL-elevating therapies are available—nicotinic acid, fibric acid derivates, statins, TZDs, bile acid sequestrants, ezetimibe—but these drugs alter other components of the lipid profile, making clinical trial interpretation difficult in assessing the effect of HDL elevation alone. Still other available drugs raise HDL but are of dubious or uncertain clinical effect upon cardiovascular outcomes. Interventions currently in development are more specific HDL elevators, but future therapies await validation in clinical trials.

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Endoscopic Ultrasound:

Indications and Applications

Sharmila Anandasabapathy, M.D.

Abstract

Since its development in the 1980s, endoscopic ultrasound (EUS) has dramatically expanded the breadth of gastrointestinal endoscopy and the approach to gastrointestinal and non-small-cell lung cancer staging. Combining an ultrasound transducer with a standard video endoscope, EUS produces detailed images of the gastrointestinal wall and structures surrounding the gastrointestinal tract. It is a safe and accurate method of diagnosing and staging a variety of benign and malignant lesions. Additionally, EUS-guided fine-needle aspiration can be performed on areas surrounding the gastrointestinal tract, including adjacent organs (pancreas, liver, etc.) and the mediastinum. The development of large channel scopes and new needles has led to numerous therapeutic applications for EUS, such as EUS-guided pseudocyst drainage. While the potential applications are many, availability of the technology continues to be a problem worldwide.

Key Words: Endoscopic ultrasound, esophageal cancer, Barrett's esophagus, lung cancer, pancreatic neoplasm, gastrointestinal endoscopy.

Introduction

Developed in the 1980s as a more accurate method of imaging pancreatic lesions, endoscopic ultrasound (EUS) has dramatically expanded the breadth of gastrointestinal endoscopy and revolutionized the staging of cancers within and surrounding the gastrointestinal (GI) tract. Over 2,000 publications have shown EUS to be a safe and accurate method of diagnosing, staging, and sampling a variety of benign and malignant lesions, including:

- Barrett's esophagus
- Esophageal cancer
- Non-small-cell lung cancer (NSCLC)
- Gastric cancer and lymphoma
- Submucosal lesions
- Pancreatic cancer
- Pancreatic cysts
- Choledocholithiasis and extrahepatic biliary disease
- Rectal cancer

The many applications of EUS rely upon its ability to visualize the various layers of the GI wall as well as surrounding organs. As its name suggests, EUS merges ultrasonography with endoscopy, allowing imaging of endoluminal structures (polyps, varices, etc.) as well as adjacent structures (liver, pancreas, mediastinum, etc.). While the endoscope permits visualization of the lumen of the GI tract, the ultrasound transducer images deep layers of the gastrointestinal wall and surrounding organs (Fig. 1). With the development of EUS-guided fine-needle aspiration (FNA), tissue diagnosis of most visualized lesions can be obtained. The following review examines some of the most frequent and validated indications for this novel technology, as well as some emerging therapeutic applications.

Indications for Endoscopic Ultrasound

Barrett's Esophagus and Esophageal Adenocarcinoma

The incidence of esophageal adenocarcinoma has increased steeply over the last several decades; it is estimated that there will be more than 13,000 new cases of esophageal adenocarcinoma diagnosed in the United States this year alone (1). Because prognosis is directly correlated with stage of diagnosis, early detection and accurate staging are critical. The development of esophageal adenocar-

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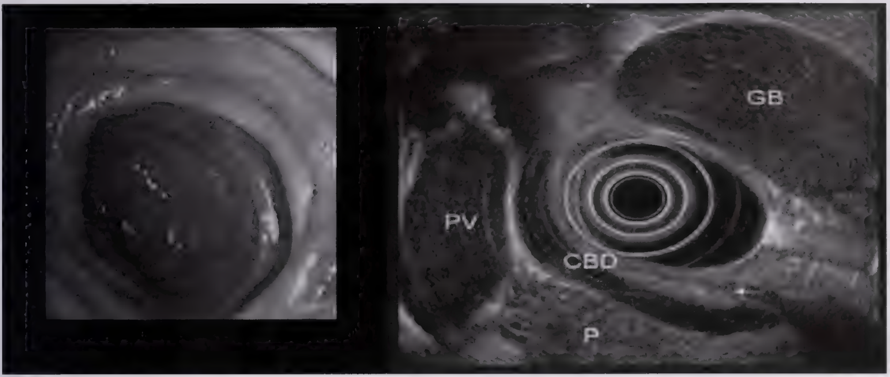

Fig. 1. Endoscopic and ultrasonographic images of the duodenum. CBD = common bile duct, PV = portal vein, GB = gall bladder, P = pancreas.

cinoma occurs through a series of progressive changes from Barrett's esophagus (intestinal metaplasia) to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and adenocarcinoma. In studies looking at surgical resection specimens from patients with an endoscopic diagnosis of HGD, carcinoma has been shown to coexist in roughly 16–30% of cases, depending upon the study (2, 3). Because of this, esophagectomy has been widely recommended for individuals diagnosed with HGD. Unfortunately, esophagectomy, despite tremendous improvements in outcomes over the last several years, remains a major operation with significant morbidity. Moreover, many individuals are poor surgical candidates. Because of this, endoscopic therapies for high-grade dysplasia have received much attention and should be considered for individuals who have high-grade dysplasia or intramucosal carcinoma. In the absence of submucosal extension, the likelihood of nodal involvement is very low, and these individuals can be safely managed with endoscopic therapy. EUS plays a critical role in ruling out submucosal involvement in patients with high-grade dysplasia under consideration for endoscopic therapy. EUS plays this role by providing detailed images of the esophageal wall; it has been shown to have a sensitivity, specificity, and negative predictive value of 100%, 94%, and 100%, respectively, for submucosal involvement (4).

For individuals who are diagnosed with esophageal adenocarcinoma itself, EUS plays a critical role in locoregional staging; EUS is usually done in conjunction with computed tomography (CT) and positron emission tomography (PET). Because the ultrasound transducer is positioned within the lumen of the esophagus and stomach, ultrasound images can be obtained without interference from bone or air to determine depth of invasion and presence of nodal involvement (Fig. 2). For locoregional staging, EUS has been shown to be significantly more accurate than CT in identifying T stage (5). A meta-analysis demonstrated an overall T stage accuracy of 89% (6). For T3 lesions, accuracy is over 90% (7). In the evaluation of nodal involvement, EUS has been shown to be accurate when EUS-guided FNA is performed on suspicious nodes. A large prospective study reported a sensitivity, specificity, and accuracy of 92%, 93%, and 92% respectively for presence of malignant lymph nodes (8).

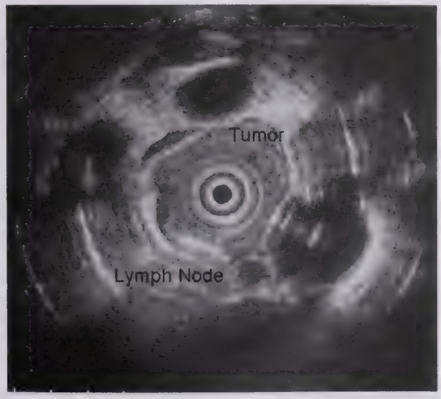

Fig. 2. Esophageal cancer with adjacent node.

After neoadjuvant chemoradiotherapy for locally advanced disease, EUS is increasingly being used to evaluate pathologic responders. Although overstaging is often an issue because of inflammatory changes and fibrosis following therapy, a reduction in tumor thickness has been shown to correlate with therapeutic response (9).

Non-Small-Cell Lung Cancer

Non-small-cell lung cancer remains the number one cause of cancer deaths in the United States. As with esophageal cancer, the stage of the disease determines the therapy, and mediastinal node involvement determines the stage. Correct assessment of direct mediastinal invasion is crucial, since it represents a clear contraindication to surgery. While CT, mediastinoscopy and bronchoscopy are typically used for staging, they have certain limitations. Mediastinoscopy is limited in its ability to reach the posterior mediastinum and bronchoscopy is often unable to access the inferior mediastinum and aortopulmonary (AP) window. EUS has been shown to have up to a 90% sensitivity in detecting lymph nodes in the superior mediastinum, AP window, subcarinal, and periesophageal regions. With EUS-guided FNA, specificity is nearly 100% (10, 11). This EUS-based approach has been shown to be cost-effective. For patients with CT-positive lymph nodes in locations accessible to EUS, the cost per year of expected survival was $1,729 with an EUS-based strategy, and $2,411 with a traditional mediastinoscopy/mediastinotomy approach (12).

Gastric Neoplasms

Though less accurate than it is when staging for esophageal cancer, EUS has been used to stage gastric carcinoma. Surgical resectability can be predicted with a sensitivity and specificity of 87.5% and 100%, respectively (13). Preoperative EUS for advanced gastric carcinoma has been shown to alter therapy in 30% of cases, usually leading to more limited resections for earlier stage tumors (T1–T3) (14). For early (T1) gastric cancers, accurate staging is critical, as endoscopic therapy can be safely performed on tumors limited to the mucosa, thus sparing the patient a gastrectomy.

For mucosa-associated lymphoid tissue (MALT) lymphomas, EUS has been shown to be very accurate both in diagnosis and staging, and in predicting outcome. Low-grade MALT with involvement of only the mucosa and/or submucosa can be treated with *Helicobacter pylori* eradication therapy, with up to an 80% response rate (15). With this strategy, chemotherapy and/or surgery can be avoided in a large number of patients. After eradication therapy, EUS can be used to monitor treatment response and to detect early relapse.

Subepithelial (“Submucosal”) Lesions

During routine endoscopy, lesions arising from the deep layers (submucosa, muscularis propria) of the gastrointestinal wall are often identified as a nonspecific “lump or bump,” invariably with an unremarkable overlying mucosa. These subepithelial lesions encompass a broad differential (Table), from benign to neoplastic conditions, and a definitive diagnosis may be impossible with standard endoscopic and radiologic imaging. EUS, by visualizing the deep wall layers and extrinsic organs, can distinguish extrinsic compression from genuine intramural lesions. By better characterizing the lesion (solid vs. cystic) and identifying which wall layer the lesion is arising from, EUS can better define the nature of the lesion (e.g., stromal tumor vs. lipoma, etc.). Additionally, FNA of deep lesions can be performed for pathologic confirmation and in instances where nonoperative treatment is under consideration (e.g., GI stromal tumor [GIST]). Small lesions (< 2 cm) arising from the mucosa or muscularis mucosa can be removed endoscopically.

Pancreatic Cancer

Currently the fourth leading cause of cancer deaths in the United States, pancreatic cancer is

TABLE

Subepithelial Lesions of the Gastrointestinal Tract

Wall Layer	Differential
Submucosa	Lipoma Carcinoid Granular cell tumor Varices Pancreatic rests Histiocytoma, fibroma Duplication cysts
Muscularis Propria	Gastrointestinal stromal tumors (GIST) Leiomyoma, leiomyosarcoma (can also arise from muscularis mucosa)
Extrinsic Compression	Spleen Liver Heart Pancreatic masses/cysts Lymph nodes

usually diagnosed at an advanced stage in which surgical resection is no longer an option. Despite advances in surgical techniques and chemotherapeutic options, five-year survival rates remain < 5% (16). Because radical surgical resections are possible only in a minority of cases and carry a significant morbidity and mortality, accurate preoperative staging is critical to avoid unnecessary operations. EUS is currently the most accurate method of locoregional staging and is superior to helical CT for determining vascular invasion and lymph node involvement (17). EUS allows close-up, detailed images of the pancreatic parenchyma, including ductal changes and dilatation, fibrosis, and calcifications. Tumor can be easily differentiated from normal parenchyma, and extension of tumor into the portal and mesenteric vasculature can be assessed to evaluate for resectability (Fig. 3). Accuracy for tumor and nodal staging is approximately 80% and 72%, respectively (18). EUS-guided FNA of pancreatic lesions can be performed with a sensitivity of 92% (19).

Pancreatic Cysts

The likelihood of a cyst in the pancreas having neoplastic potential is greater than that for cysts in other organs. Pancreatic cysts span the histologic spectrum from inflammatory lesions (pseudocyst), to benign lesions (serous cystadenoma), premalignant lesions (mucinous cystadenoma), and malignant lesions (intraductal papillary mucinous tumor, mucinous cystadenocarcinoma). EUS can provide detailed images of pancreatic cysts, but cannot, on appearance alone, reliably distinguish between benign and malignant ones. Interobserver agreement is low and morphologic criteria alone are nonspecific (20). With EUS-guided FNA, and analysis of cyst fluid markers, these limitations can at least partly be overcome. In a multicenter study, Brugge et al. prospectively looked at EUS imaging, cyst fluid cytology, and cyst fluid tumor markers (CEA, CA 19-9, CA 72-4, CA-125, CA 15-3) in a wide range of cystic lesions. With histology as the diagnostic standard, the accuracy of cyst fluid CEA (79%) was significantly greater than that of EUS morphology (51%), cytology (59%), and other diagnostic tests combined, in differentiating mucinous from nonmucinous cystic lesions (21).

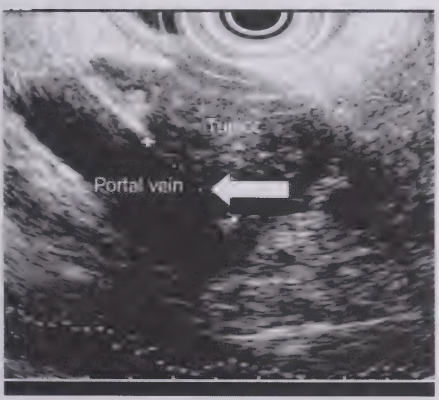

Fig. 3. Pancreatic head tumor with invasion of portal vein (arrow).

Choledocholithiasis and Extrahepatic Biliary Disease

Because of the proximity of the duodenum to the gallbladder and bile duct, EUS is an ideal method for evaluating diseases of the extrahepatic biliary tree (choledocholithiasis, unexplained dilatation of the common bile duct, etc.). The sensitivity of EUS for the diagnosis of choledocholithiasis is >95%, a rate roughly equivalent to that of endoscopic retrograde cholangiopancreatography (ERCP), and equivalent or slightly better than that of magnetic resonance cholangiopancreatography (MRCP) (22). Because the complication rate is markedly lower than for ERCP (23), EUS should be performed before ERCP in individuals with an intermediate probability of common duct stones, with ERCP reserved for those who have a high probability of harboring stones. In institutions that have EUS capabilities and can perform EUS and ERCP sequentially, an EUS-centered approach is the most cost-effective approach to the management of choledocholithiasis (24).

Rectal Cancer

Unlike colon cancer, for which locoregional staging plays no role, rectal cancer management is directly guided by local staging. EUS is used routinely in the preoperative staging of rectal cancer to determine whether neoadjuvant therapy is appropriate (25). Although EUS is often used for restaging after neoadjuvant therapy, this practice is controversial, since the accuracy of EUS after radiotherapy is markedly reduced (26).

Therapeutic EUS

The development of large channel echoendoscopes, new and larger needles, and refinements in technique have led to numerous advances in interventional or therapeutic EUS.

Communications can be made between the GI tract and other organs under EUS guidance. Giovannini et al. described the creation of a hepaticogastrostomy under EUS guidance in a patient with inoperable hilar tumor (27). Pancreatic pseudocysts and abscesses can be drained using large channel echoendoscopes and stents to create a communication between the stomach and pancreas (28). Directed antitumor therapy using a needle advanced under real-time imaging is an evolving frontier. Additionally, EUS is being used in phase I and II clinical trials, to inject cytokine directly into pancreatic cancers. For patients with intractable pain due to pancreatic cancer or chronic pancreatitis, EUS-guided celiac plexus neurolysis has been shown to significantly reduce pain scores (29, 30).

Conclusion

Endoscopic ultrasound has dramatically extended the reach of gastroenterology, moving endoscopists beyond the lumen and into adjacent organs and the mediastinum. Additionally, EUS has radically impacted the approach to cancer staging of gastrointestinal malignancies. Despite all this, EUS is highly operator dependent and only available in a limited number of predominantly high-volume medical centers. Moreover, the results published to date have come largely from these high-volume referral centers. Thus, the above studies should be interpreted with some caution. Despite these shortcomings, the past two decades have seen tremendous improvements in the accuracy of EUS. With further improvements in technique and technology, the potential applications seem to be limitless.

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Medical Police and the Nanny State:

Public Health versus Private Autonomy

JEREMY HUGH BARON, D.M., F.R.C.P., F.R.C.S., F.R.C.P.G.

Abstract

Rome tried to increase both the numbers of its people and their well-being, and hence their wealth, but it was not until the 16th century that European rulers were urged to achieve these aims by the power of the state to enforce public health. By the 17th century, absolutist states such as France, Austria and especially Germany had created an administrative profession of enlightened despotism, with "medical police" to encourage healthy and thus wealth-producing citizens. Johann Peter Frank (1745 – 1821) was the profession's exemplar with his 6,262 page *System einer vollständigen medicinischen Polizey*, leading to comprehensive public health legislation in German-speaking states, followed by more libertarian countries such as Britain and the United States. However, controversy continues on the role of government in trying to save its citizens, and especially their children, from harming themselves and/or others by their actions and omissions.

Key Words: Public health, Europe, US, Johann Peter Frank, immunization, alcohol, autonomy.

ADVANCES IN clinical science and technology make it possible for most of us to live long and healthy lives. However, some people may not wish to seek or take advice for healthy living, so for thousands of years states have made laws to protect (or enhance) the health of individual citizens and of society as a whole.

Lawrence Gostin has written about the conflict between individual rights and social well-being in the U.S., and has questioned the primacy of individual freedom (1). I therefore present here the historical background of compulsory public health, both in Europe and North America, and explain why, in health-related controversies involving the state and the individual, I lean towards individual autonomy.

Welfare of the State

In ancient Rome, Cicero expressed his populist sympathies when he stated that *"salus populi suprema lex"* (the well-being of the people is the most important rule) (2). George Rosen has analyzed in detail how, beginning in the sixteenth century, several European countries decided that the welfare of the state as a whole was equivalent to the welfare of its people: the more numerous and the healthier its population, the greater the power and wealth of the monarch and the state (3 – 6). For simplicity, individual citations have not been provided in the next seven paragraphs because they are available in Rosen's texts (3 – 6).

France

Louis XIV of France was one of the first monarchs to attempt practical measures to increase public welfare. To increase Canada's population, Louis' finance minister Colbert ordered its governor in 1668 to produce an additional 200 families annually, by a law exempting early marriages from taxes, and fining fathers whose girls were still single by 16, or whose sons were still single by 20.

The military engineer Sebastien Vaubin organized detailed censuses of the parishes of France in 1697, and in 1711 the Abbé Fleury used the term "medical police." But in spite of many proposals in the eighteenth century to reorganize French medical and social care, attempts at implementation had to wait until the Revolution (3, 4).

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Great Britain

In 1648, Dr. William Petty proposed a Council of Health and a 1,000-bed teaching hospital; he also created the "science of political arithmetic" and recommended the "multiplication of mankind." He analyzed the Dublin bills of mortality and calculated that if a quarter of the 360,000 annual British deaths could be prevented, "the King will gain and save 200,000 subjects per annum, which valued at 20 £ per head, the lowest price of slaves, will make 4 million per annum benefit to the Commonwealth." Queen Anne was advised in 1707 of "the Means of Multiplying Your Majesties People," and in 1714 that "regularly laboring people are the Kingdom's greatest Treasure," or in Defoe's even simpler axiom, "The more mouths, the more wealth." None of these proposals came to fruition in decentralized Britain until the 19th century.

Germany

In 1556 the Elector of Saxony was advised to promote good, godly government by the judiciary and police. The German *Polizey* (or *Polizei*, etc.) comes from the Greek *politeia*, administration of a state. Similarly, in English "police" in the 18th century meant civil administration, and only in the 19th century was it used, as today, for the constabulary. *Medicinische Polizei* is inevitably, but confusingly, translated literally as "medical police," conjuring up a sinister world of physicians acting as policemen, and/or uniformed policemen acting as health inspectors. But the term "medical police" originally meant public health administration, and in 1610 a 1,350-page text recommended that public health be controlled by a "Christian police." In 1617 Emperor Rudolf II was advised on *Policey-Ordnung und Constitution* (that is, constitutional arrangements), including population statistics, and the state of Gotha was advised to provide complete medical and social care by public health administrative, *Polizey Wissenschaft*. A German physician in 1668 suggested a bureau of public health to increase population and wealth, as did his Austrian brother-in-law. Leibniz in 1678 followed Petty in recommending political topography (the natural resources and population of each district and its health statistics) to the Duke of Hanover, and in 1680 advised the Emperor to set up a medical authority. As in Britain, the governments of these states implemented few of these proposals.

However, in 1685 Prussia set up a *Collegium sanitatis* in 1685, and in 1688 began to issue health statistics; in 1727 it created two professorships to train civil servants in the political and economic sciences as an administrative profession for enlightened despotism including improving public health. The Ulm municipal physician found health education difficult because "no one reads anything," and suggested advising the people in the popular almanacs.

Austria

Austria followed Germany's example in 1750, when Empress Maria Theresa adopted a system in which public health became part of the policing of her peoples as an arm of the state. In 1763 she created a chair for Joseph von Sonnenfels, who wrote the two-volume *Grundsätze der Polizey, Handlung und Finanz* (fundamentals of public administration, commerce and finance), published in 1765. He advised Maria Theresa and her successors Joseph II and Leopold II, that authoritarian prosperity could also be humanitarian. The subject of public health soon was taught at many universities and was the subject of dissertations by medical students.

The Empress influenced the health of her people by a *Protomedicus*, or director of public health, who from 1745 was Gerard van Swieten, her personal physician. He persuaded the Empress that the Faculty of Medicine needed a new, university-controlled general hospital in Vienna, to be the finest hospital in the world for the best teaching, research and patient care. He also persuaded her that patients would be admitted to this *Allgemeine Krankenhaus* only if they agreed to accept the medical treatment or surgery recommended for them, and that if they died a *post mortem* examination would be done.

Johann Peter Frank—Father of Public Health

Frank was born near Lake Constance in 1745. His grandfather was French, his father a trader and his mother a mayor's daughter. He obtained a doctorate of philosophy in France, and his medical doctorate in Heidelberg in 1766. At age 21, the new doctor told Dean Oberkamp, a pupil of Boerhaave, that his ambition in life was to study, prevent and/or treat those diseases that affected most people, and that these diseases were mostly preventable because they were rooted in social conditions. Frank, who named his brainchild *medicinische Polizey*, has been considered the father of public health precisely because he tried "to prevent evils through wise ordinances." (More detailed information and source materials on Frank and his life's work can be found in references 7 and 8.)

Few physicians have ever made such bold claims, at so young an age, and then lived to see their plans accepted internationally. Frank began as a country doctor for two years and then became a district medical officer in Baden in 1768, from where he sent the first volume of his *Medical Police* to a publisher in Karlsruhe. Frank's manuscript was rejected, and he was said to have burnt it and waited 11 years before trying again. In 1769 he became physician to the Prince-Bishop of Speyer and was able to study the ills of the serfs. He saw that peasants froze because they were forbidden to cut wood from forests to warm themselves; and that they were forced to neglect their fields to act as beaters for hunting by their masters. Children were crippled by hard labor, and then taken as soldiers at 16, leading to decrease in population. Mothers had to work in the fields at harvest, neglecting their babies (who were sometimes eaten by pigs). Frank knew that a mare had twelve weeks' rest in pregnancy, and he wondered why a woman should not have a similar benefit. He established two hospitals and schools of surgery and midwifery.

In 1779 he asked many experts the practice and laws of public health in their own states and published in Frankfurt the first volume of his magnum opus, *A System of Complete Medical Police* (*System einer vollständigen medicinischen Polizey*) (8), covering marriages, dowries, fertility, pregnancy and child-bearing. Fertility was to be enhanced by the physical education of young women, who were not to be mistreated, nor beaten when pregnant, but cared for by trained, salaried midwives. Children were to be cherished and breastfed by their mother or a licensed wet-nurse. Frank proposed a ban on corsets because "the thoracic cavity was not created by the Creator to the taste of us Europeans." Frank promoted public amusements, but plays were to avoid a stage full of murders (as in England, leading to melancholia), or heroes and heroines killing themselves (as in France, encouraging suicide).

Frank's second volume, in 1780, described intercourse, venereal diseases, abortion and prostitution. The third volume, in 1783, discussed air pollution; nutrition (control of food, water and alcohol); public paving and cleansing; unhealthy and dangerous trades; clothing, sumptuary laws and housing; and drainage and latrines. Frank admired Moses for his public health laws, including his provision for quarantine for diseases thought to be infectious (Lev. 13.1–45) and his rule that every Israelite relieving himself outside the camp should have a little shovel to cover his excrement with soil (Deut. 23.13–14).

In 1784 Frank became professor of clinical medicine in Göttingen, and then in 1785 moved to Pavia as *Protophysicus*, directing public health for Lombardy and Mantua, as well as revising the curriculum for doctors, midwives and apothecaries. His fourth volume, in 1788, on public safety, proposed laws on preventing people being crushed by crowds; on unsafe buildings and scaffolding; on fires and road injuries; and for police inspection of carts and hackney carriages. He also published the first of a six-volume textbook in Latin of medical treatment, *De curandis humanum morbis epitome*.

In 1795 Frank succeeded van Swieten as professor of clinical medicine in Vienna. He took all the medical beds for teaching and research and revised the curriculum. His fifth volume, in 1812, dealt with resuscitation and funerals. In 1799 a public health officer in lower Austria vaccinated his three children with Jenner's cowpox, so Frank arranged a public vaccination test in his unit in 1801. The trial was successful, leading to Austria's Vaccination Law of 1808. However, Frank never became Protomedicus, because in 1804 the faculty ousted him for unfolding to his students a whole complex of scientific problems and allowing them to form their own opinions rather than following the orthodox textbooks. Frank did not endear himself to colleagues by statements such as the following:

> The greatest art of the teacher of medicine is to protect his students in time from the dangerous delusion that merely speculative statements are certain, to teach them to doubt everything that is not confirmed by mature experience, and to acquaint them with the gaps, with the known limits of the art, as well as with the best sources from which they can obtain truth in the future also (9).

Frank then worked in Vilna, St Petersburg and Frankfurt, before returning to Vienna in 1811 to write more volumes and new editions of his *Medical Police*, to a total of 6262 pages. The sixth volume, in 1816, covered medical affairs, and was followed by supplementary volumes on hospitals and administration. Frank died in 1821 with no illusions about the unpopularity of his ideas. In the 1783 revision of volume 1, he noted that

> it is incomprehensible to me how anyone can hope to retain natural freedom in political life without curbs. And it seems to me that is philosophizing à la Rousseau.... I understand the objections well, people want fewer laws, and with the few laws they want to retain their complete freedom—but is this not a complete contradiction? ... The common people, as long as they lack the necessary enlightenment, ulti-

> mately cooperate in the public health arrangements prescribed by the state only under duress, and as soon as they can evade state supervision (faithful to their old, though, obviously deleterious habits) they thwart them (8).

After Frank

Frank's published master plans certainly encouraged comprehensive public health legislation in German-speaking countries and neighboring Switzerland and Italy, and eventually led to the social insurance reforms of the 1880s in Austria and Bismarckian Germany (10).

Great Britain

Frank's authoritarian, planned public health did not export easily to more libertarian countries. Thus, although the new voluntary hospitals and public dispensaries helped the sick "respectable poor," and although the Gin Acts of 1751 did license places for sale and consumption of alcohol, communal public health legislation had difficulties in passage through Parliament. In 1802 Peel's Law restricted children's work in cotton mills, but it was not until the Factory Act of 1833 that children under 9 were forbidden in factories, and for the first time there were inspectors to enforce such regulations, with medical inspectors for the Poor Law Commission in 1838 (11). The 1842 Mines Bill banned women, and children under 10 years old, from working in the mines. Liverpool in 1846 passed the first Sanitary Act and employed a medical officer of health, a borough engineer and an inspector of nuisances to enforce anti-nuisance, sanitary and zoning laws. The 1848 Public Health Act did create a national General Board of Health, but that was discontinued in 1874.

England's general *laissez-faire* attitude persisted, with *The Times* boasting in 1851 that "Aesculapius and Chiron...have been deposed, and we prefer to take our chance of cholera and the rest than be bullied into health." As late as 1897, after a series of typhoid epidemics causing 40 deaths in King's Lynn, it was reported that "the people of Lynn have little taste for pure water. They evidently prefer sewerage and they like it neat" (12).

Although the concept of medical police never reached England's two universities, it quickly took root in Scotland, where Edinburgh had lectures on forensic medicine and medical police at least from 1795, a professorship there in 1807, and then a similar chair in Glasgow.

The United States

The U.S. preceded Great Britain in establishing a Board of Health in New York City in 1805. However, health legislation was opposed by American libertarians such as Mark Twain, who in 1867 warned that

> the mania for giving the Government power to meddle with the private affairs of cities or citizens is likely to cause endless trouble... and there is great danger that our people will lose that independence of thought and action which is the cause of much of our greatness, and sink unto the helplessness of the Frenchman or German who expects his government to feed him when hungry, clothe him when naked, to prescribe when his child may be born and when he may die, and, in fine, to regulate every act of humanity from the cradle to the tomb, including the manner in which he may seek future admission to paradise (13).

In 1866 the New York Academy of Medicine led a campaign to establish the Metropolitan Board of Health, but a national board was not formed until 1879, and it lasted only four years. However, when public health laws were eventually codified in 1892, the U.S. legitimized compulsion with statements that Frank would have approved of: "It needs no argument to prove that the highest welfare of the State is subserved by protecting the life and health of its citizens by laws which will compel the ignorant, the selfish, the careless and the vicious, to so regulate their lives and use their property, as not to be a source of danger to others" (14). By the beginning of the twentieth century, New York boasted the finest public health of any city in the world, and its Board of Health's motto was "Public Health is purchasable. Within natural limitations every community can determine its own death rate" (15).

Public Health Laws

Cities and nations need laws to protect their citizens from dangers. Causing death by unsafe building was a capital offense in the Code of Hammurabi. Exodus 21:33–34 calls for monetary compensation "when a man opens a pit or digs a pit and does not cover it." Deuteronomy 22:8 requires that "when you build a new house, you shall make a parapet for your roof; otherwise you might have bloodguilt on your house, if anyone should fall from it." Cicero listed the Roman republic's laws and noted that they were not self-enforcing. The consuls appointed public officials called aediles to control baths and taverns, gambling, fire precautions, quality of provisions, sewers and aqueducts, street cleaning and paving, sumptuary laws, traffic and dangerous buildings and animals (16). Almost all developed states have similar laws, but not all appoint inspectors.

Driving

The public accepts many health regulations, but has been particularly reluctant to obey laws against dangerous driving and dangerous vehicles. In his day Frank commented that "any fop… may consider himself entitled to grandly run down any creature who is lowly to him." In his Vienna, the four-lane bridge to the Prater (a public park) had the outer two reserved for pedestrians, and the middle two for carriages going and returning. Hussars with drawn sabers controlled the traffic. Even aristocrats were liable to fines, house arrest and a permanent ban on driving within the Austrian states.

It took decades to persuade legislators to compel manufacturers to fit cars with fixtures for seatbelts, then for all cars to be sold with belts in both front and back seats, and finally for them to be worn, with special restraints for babies and children. Too few countries have such laws, and in many countries they are ignored. Passengers who refuse to wear seatbelts ("It's my funeral") are unaware that belted occupants are at an increased risk of injuries and deaths from unbelted passengers in the event of a collision (17). Fortunately, motorcyclists who are not wearing a helmet are more easily detected and prosecuted. Regulations on child safety, such as helmets for bicyclists and skateboarders, are opposed by those who "saw this law chipping away at civil liberties and parents' rights to raise their children the way they want to" (18). Riding schools may require horse riders to wear approved helmets, but legislation is unlikely in Britain, because its monarch rides hatless.

Citizens and Their Children

I can accept the view that people are entitled to risk harm to their own health and shorten their lives by ignoring governments' warnings on excess alcohol, cigarettes and unhealthy foods. To me the principal bioethical problem is the state's choice of interventions on behalf of their children. Most bioethicists today follow John Stuart Mill, who asserted that "Power can rightfully be exercised over any member of a civilized society against his will [only] to prevent harm to others" (he excluded the immature). Governments override Jehovah's Witness parents denying life-saving blood transfusions for their children.

Several European countries even protect children's mental welfare by preventing their being given silly or preposterous names that might ridicule them in childhood and lifelong; Denmark's Law on Personal Names is one of the strictest, with only 3,000 names authorized for boys and 4,000 for girls (19).

Immunization. Tests for genetic disorders and multiple courses of immunization of babies and children require parental cooperation and consent, so that complex protocols and timetables can be followed. When an infant misses one or more of its injections, not only is the child at high risk of catching, and even dying from, the particular microbial disease, but the whole community is more susceptible unless the percentage of those immunized is almost complete. Yet the Dutch government accepted religious objections to poliomyelitis immunization, resulting in outbreaks of this disease in the village of Staphorst in 1971 and 1978 (20).

Vaccination by compulsion in Austria (from 1808) was copied by many states in the 19th century, and although it was generally accepted as preventing and controlling outbreaks of smallpox, there were inevitably complications and deaths, especially from tetanus, and mostly from poor technique. A sophisticated public rightly demands evidence for the efficacy and safety of immunization campaigns.

Vaccination with live cowpox against smallpox came to America in 1801, and by 1809 Massachusetts made it compulsory for all adults, for infants, again at entry to public school, and again for all adults during an epidemic (21). Few states had such sweeping powers. However, at the end of the 19th century, in Brooklyn (then a separate city from New York), coercive measures included putting a yellow flag outside an infected house, with police officers preventing anyone from entering or leaving, together with nocturnal sweeps by immunizing teams of police-guarded vaccinators (22). Legal challenges in the United States were frequent, but were finally squashed by the Supreme Court in 1905 (23). Justice Harlen may not have read Johann Peter Frank's books, but he used the identical argument: "There are manifold restraints to which every person is necessarily subject for the common good. On any other basis organized society could not exist with safety to its members. Society based on the rule that each one is a law unto himself would soon be confronted with disorder and anarchy" (23).

Since then there have been several worrisome immunization campaigns in the U.S. In 1976 President Ford, on the advice of the Department of Health, obtained $135 million from Congress for a national immunization program with a swine influenza strain, chosen to resemble the strain responsible for the 1918 pandemic. The program was suspended because of a ninefold increase in Guillain-Barré syndrome. A live oral poliomyelitis campaign produced paralysis in 1 of 2.6 million doses (and 1 of 750,000 initial doses), so that only inactivated poliovirus is now used for children in the U.S. (24).

In such controversial situations even the experts may change sides. Thus, in 1914 Hermann Biggs, an important figure in public health in New York City and State, was faced with a smallpox outbreak in the city of Niagara Falls, an area opposed to vaccination by the state law (which was not universally obeyed throughout the state). Biggs ordered vaccination of many schoolchildren in the state, resulting in several deaths, including the child of a prominent legislator. These deaths led to a bill to remove compulsion from vaccination programs. Most medical experts opposed such a bill. Biggs surprised everyone by not opposing that legislation. He argued that smallpox had become so rare that (rural) routine vaccination was unnecessary except when faced with an epidemic. Moreover, he had decided that "the keynote of modern public health work is public education—not compulsion. Success comes from leading and teaching, not from driving people" (25). Compulsory immunization of everyone is impossible, but Colombia and Mexico have tried to transfer money to poor families only if their children receive preventive health care, enroll in school and attend classes.

Sex Education. Sex education in British schools is rare and ineffective, perhaps one factor in the teenage pregnancy rate of 20 per thousand being the highest in Europe, and five times the rate for Dutch children, who are taught about condoms for boys and contraceptive pills for girls (26).

Alcohol and Cigarettes in Britain

There are laws to prevent children from buying alcohol and cigarettes, but the problem for volitional adults is unsolved. States can control each of these health risks by fixing the price through taxation, and controlling the number of sites of consumption by licensing laws. Britain was once particularly successful with these problems, but no longer.

Alcohol. In World War I the British Central Control Board of Liquor Traffic halved spirit consumption and reduced beer intake from 25 to 10 gallons per capita, with convictions for drunkenness falling from 136,000 to 39,000 annually (27). In the last half-century alcohol, especially spirits, has become relatively cheap through tax reduction, beers are now stronger, points of purchase have multiplied, and licensing hours of pubs have been extended (up to 24 hours per day). Britain is aswill with alcohol and its many disease complications. Speeding by young men, and older men wanting to feel young, in ever-heavier and more powerful cars and motorcycles, often after alcohol, or distracted by handling mobile telephones, is common and lethal. Speed limits are disobeyed because "I can drive safely at any speed." Police traps, video cameras and breathalyzers are condemned as spying, even though speed cameras are effective in reducing road traffic collisions and their associated injuries and deaths (28). Motorists, after their arrest and trial, are too often acquitted by motoring magistrates and jurors.

The 1961 Road Traffic Bill set the safe blood alcohol level at 160 mg per 100 ml, perhaps equivalent to drinking two-thirds of a bottle of whisky. This level was cut to 80 mg in 1965; it should be 50 or less. Recent British governments have ignored warnings of the dangers of alcohol. In 1979 the Cabinet's own Central Policy Review Staff gave so bleak a picture of the harm to the country from alcohol, and how urgently action needed to be taken to prevent the situation from worsening, that the government, mindful of the alcohol industry, its half million employees, and its tax revenues, banned publication of the draft report. Fortunately, a copy was leaked to Sweden, and copies smuggled into Britain from there (29). The Government's published document, *Drinking Sensibly,* simply recommended education (30), and the latest White Paper (31), some 23 years later, promises little to cut alcohol consumption (32).

Cigarettes. Cigarettes are still advertised in England, and its government has yet to follow California, New York City, Cuba, Ireland and Scotland in banning smoking in all public places, to at least lessen passive smoke damage to non-smokers (33).

Food and Water

Fortification of public water and food ingredients has been hotly contested. Most local authorities in the U.S., and many other countries, chlorinate reservoir water to destroy pathogens, and this practice has gradually been accepted by the public. Fluoridation of water to prevent dental caries in children is so violently opposed in Britain that its use is subject to local option. Countries with high incidences of iodine-deficiency goiter have solved this problem by fortifying all salt with iodine. Rickets can be prevented by fortification with vitamin D. Britain fortified flour with iron to prevent iron-deficiency anemia, but I have never been convinced that the added inorganic iron is actually absorbed. Spina bifida and other neural tube defects in babies are mostly due to folic acid deficiency in pregnant mothers, and could be prevented if mothers took tablets of this vitamin regularly, probably an unreachable goal. Canada, but not Britain, fortifies white flour, pasta and cornmeal with folic acid and has almost eliminated these neurological defects (34). General laxity has been the response of governments and educational authorities to the alarming increase in adult and childhood obesity from excess eating of high-fat foods and sugary drinks. No ban on their advertising is likely, merely a plea to food manufacturers to reduce promotion of unhealthy foods at times when children view television. Schools should provide plenty of drinking water fountains, and not be allowed to make money by selling sugary drinks or "junk food."

Emergency Health Powers in the U.S.

Lawrence Gostin, professor of law at Georgetown University, Washington, and professor of public health at Johns Hopkins, a former head of the British National Council of Civil Liberties in the 1970s, and of the Privacy Committee of the American Civil Liberties Union, wrote in the preface to his 2000 text, "Despite my background as a civil libertarian, in this book I question the primacy of individual freedom (and its associated concepts—autonomy, privacy and liberty) as the prevailing social norms" (35).

I suspect that the staff of the U.S. Centers for Disease Control and Prevention (CDC) were familiar with these revised opinions of Gostin when, in Spring 2001, they chose the Georgetown-Hopkins Center for Law and the Public Health to draft a Model State Emergency Health Powers Act that "gave governors or health officers additional authority to compel action by patients, potential patients, professionals or providers" (36). After the 9/11 attacks and the anthrax cases in October of 2001, the CDC posted a draft on the Web and revised it in December; it was then endorsed by the Secretary of Health and Human Resources. By 2002 more than 34 states had introduced legislation inspired by this draft model. Civil libertarians have denounced these acts for "blatant disregard for personal privacy and individual liberties" (36).

Conclusion

In the debates over public health and individual liberties, I have reached my own conclusions. Although there are few despotic developed countries, I did spend two years in the British army, where soldiers, irrespective of their own opinions, are compelled to protect themselves from diseases by undergoing immunization, using prophylactic condoms and ingesting tablets. I ordered soldiers to be admitted to the hospital, where they stayed until I ordered them out, to be ordered to return to my clinic for follow-up. If an officer was given two weeks' convalescence leave, and he told me he needed to get back to his men in the jungle, I simply explained that my recommendation was an order, not a suggestion. Soldiers were ordered to take their anti-malaria tablets, and if they did catch malaria, I had to recommend disciplinary action, because it was assumed they had not swallowed the tablets administered each morning by their sergeant. When I was sent to cope with cases of smallpox, I could easily prevent an epidemic by immediately cordoning the site with a fence and armed sentries, and by revaccinating all the contacts, including myself.

However, an educated and informed population increasingly resists the enforcement of public health mandates. Recently, American soldiers disobeyed military orders and even successfully appealed to civilian courts against their having been disciplined, for refusing injections of an anthrax vaccine. They won their case because this old vaccine had been designed, prepared and tested against skin anthrax, and perhaps had never been tested for efficacy against the lethal inhaled pulmonary anthrax (37, 38).

The battle between those who would improve public and private well-being by medical police, against those who regard a "nanny state" as a harbinger of a police state has raged, still rages and always will.

I certainly see, and have personally used, all the advantages of medical police, and understand Gostin's querying of individuals' freedom to refuse safe and effective vaccines. Nevertheless, I am far more concerned, both in my winters in the U.S. and in my summers in Britain, that our nanny states might turn into police states, and on balance I therefore choose education, however inefficient, rather than compulsion, to prevent private ill-health and promote public well-being.

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Pulsed Radiofrequency for the Treatment of Ilioinguinal Neuralgia after Inguinal Herniorrhaphy

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Abstract

Background and Purpose: Ilioinguinal neuralgia secondary to inguinal hernia repair is frequently a chronic, debilitating pain. It is most often due to destruction or entrapment of nerve tissue from staples, sutures, or direct surgical trauma. Treatment modalities, including oral analgesics, nerve blocks, mesh excision, and surgical neurectomy, have varied success rates. Pulsed radiofrequency (PRF) has recently been described as a successful method of treating chronic groin pain. Unlike conventional radiofrequency, PRF is non-neurodestructive and therefore less painful and without the potential complications of neuritis-like reactions and neuroma formation. Although the mechanism is unknown, it appears that the interaction of an electromagnetic field and c-fos proteins may alter normal transmission of painful impulses. Our study examines five patients treated with PRF for ilioinguinal neuralgia secondary to inguinal herniorrhaphy.

Method: Five patients were diagnosed with chronic ilioinguinal neuralgia secondary to inguinal hernia repair at our institution. Each patient was treated at vertebral T12, L1, and L2 with root PRF at 42°C for 120 seconds per level.

Results: Four out of five patients reported pain relief lasting from four to nine months on follow-up visits. Only one patient reported no pain relief whatsoever.

Conclusion: Ilioinguinal neuralgia is challenging to treat. We have demonstrated the successful use of PRF for four out of five patients seen in our office.

Key Words: Pulsed radiofrequency, groin pain, ilioinguinal neuralgia.

Introduction

APPROXIMATELY 700,000 inguinal hernia repairs are performed annually in the United States alone (1). Although the operation is relatively safe and is routinely performed worldwide, chronic postoperative inguinal pain can be an unfortunate sequela. In the inguinal region, innervation is supplied from T11–L2 nerve branches, which may be damaged or entrapped by staples or mesh during surgical repair, causing paresthesias (2, 3). Although the exact incidence of chronic postoperative pain is unknown, a recent review of reported cases revealed an incidence complicating 0–53% of herniorrhaphies (4). Morbidity from chronic pain can be severely debilitating and difficult to treat, thereby posing a serious problem to patients and health care workers alike. Our report specifically addresses postoperative ilioinguinal neuralgia occurring from damage to the ilioinguinal nerve, and its treatment with minimally invasive pulsed radiofrequency.

Ilioinguinal neuralgia (T12–L1) is characterized by burning pain through the lower abdomen radiating to the superior medial thigh and to the scrotum or labia majora. A positive Tinel's sign may be present, in which the pain may be reproduced by tapping the affected area or extending the hip and thigh. Similarly, genitofemoral neuralgia (L1–l2) presents with pain in the inguinal region radiating to the superior medial thigh and genitals. Unlike ilioinguinal neuralgia, a Tinel's sign cannot be induced. Differentiation of the two may prove difficult, as anatomic variability sometimes allows for communication between the two nerves. Nerve blocks may be performed on either nerve to see if pain relief results, thus indicating which nerve is involved (2).

Treatment modalities are wide and varied. Pharmaceutical options range from oral analgesics to transdermal patches that often yield inconsistent results. Nerve blocks may be utilized to relieve pain and elucidate the origin of pain, yet they are only temporary measures. Surgical intervention in-

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cludes re-exploration, mesh excision, and neurectomy. Although favorable results have been reported, patients are subjected to the risks of additional surgery and anesthesia. Furthermore, mesh extraction can be tediously difficult and neuritis-like reactions have been reported following neurectomy (3). Other complications reported include areas of hypoanesthesia and loss of cremasteric reflexes following reoperation secondary to groin pain (2). Radiofrequency (RF) has long been used as a neurodestructive treatment for severe pain; in this procedure a constant high frequency (500kHz), high temperature (80–82°C) electrical current is applied to target tissue via electrode. The high temperature achieved with RF is neurodestructive, thus preventing the propagation of pain signals. RF is characterized by a four-to-six-week period of discomfort occasionally marked by hypoanesthesia and neuritis-like reaction, followed by return of normal sensation and reduced pain (5). Furthermore, pain may potentially worsen, as nerve regeneration may lead to neuroma formation. Neuromas can increase sympathetic discharge and exaggerate the normal response to stimuli, leading to hyperalgesia, allodynia, and dysesthesias (6).

Pulsed radiofrequency (PRF) has gained popularity in recent years as an alternative to conventional RF. Unlike RF, which delivers a continuous current of electricity, PRF delivers high intensity currents in pulses, allowing heat to dissipate during the latent period so that neurodestructive temperatures are not reached and neuritis-like reactions do not occur. Tissue temperatures do not exceed 38–42°C, below the 45°C temperature documented for cellular damage (5). A 500 kHz current is applied with 2 bursts/second, with each pulse lasting 20 msec over a 120 second interval. Favorable outcomes have demonstrated improved results with PRF compared to RF; the exact mechanism of PRF remains unclear (7). Current studies are examining the role of cellular protein expression induced with PRF as compared to RF (8). Other studies suggest that an electromagnetic field (EMF) is created during the active phase of PRF and that the EMF causes a cellular change that favorably alters the transmission of painful impulses. PRF is relatively painless in comparison to conventional RF and has been reported to successfully treat chronic joint pains in the back, neck and hip, as well as neuropathic pain.

Methods

The five patients discussed below were diagnosed with chronic ilioinguinal neuralgia secondary to open inguinal hernia repair at our institution. Each patient was treated at vertebral levels T12, L1, and L2 with root PRF at 42°C for 120 seconds per level.

Case Reports

A 56-year-old male with a history of left-sided ilioinguinal neuralgia for the two years following a left-sided open inguinal hernia repair successfully underwent a left-sided T12, L1–L2 root PRF. He reported 80–90% pain relief lasting for approximately four to six months.

A 47-year-old female with chronic ilioinguinal neuralgia for the 3 years following left open inguinal hernia repair underwent a left-sided T12, L1 pulse root radiofrequency. She reported approximately 95% pain relief, which lasted for six months.

A 39-year-old male, approximately one year after right open inguinal hernia repair and subsequent right-sided groin pain, underwent a successful right-sided T12, L1–L2 pulse radiofrequency of the roots with an eight-month period of pain relief.

A 58-year-old male, approximately three and a half years after left-sided open inguinal hernia repair with subsequent left ilioinguinal neuralgia, successfully underwent a left-sided T12, L1–L2 pulse radiofrequency with a nine-month period of pain relief.

A 42-year-old female, three years after right open inguinal hernia repair, with a subsequent right ilioinguinal neuralgia, underwent a right-sided T12, L1–L2 pulse radiofrequency with no pain relief whatsoever.

All patients were evaluated in our offices following treatment with PRF. Patients whose pain symptoms were initially alleviated by PRF were noted to have less severe pain following the return of their symptoms, and they have been satisfactorily treated by oral medications to date. The one patient who received no relief with PRF terminated further follow-up after determining that the treatment had been unsuccessful.

Discussion

Chronic, debilitating groin pain may result from a myriad of etiologies, including blunt trauma to the lower abdomen, surgical trauma or nerve destruction, nerve entrapment by mesh, suture, or adhesion, tissue tension and ischemia from the repair itself, and neuroma formation after regeneration of a cut nerve (6, 9). There have been conflicting reports as to whether the use of minimally invasive surgery is more or less likely than open procedures to predispose a patient to chronic postoperative pain (4). Factors that appear to increase the risk of postoperative chronic pain include reoperation for a recurrent hernia, ambulatory surgery, preoperative groin pain, visible bulge and numbness in the surgical field postoperatively, and prolonged recovery time (4). Early identification of high-risk patients may facilitate prompt treatment, avoid unnecessary suffering, promote the return to an active, productive lifestyle, and prevent any negative psychological effects from chronic pain.

Although we have experienced excellent resolution of ilioinguinal neuralgia with PRF, the mechanism of action is still unclear. Selective nerve fiber destruction with the use of RF and PRF remains an area of controversy. Experiments on cat saphenous nerves originally indicated that small delta and unmyelinated C fibers were preferentially destroyed by RF (10). Later experiments, however, showed that RF lesions do not differentiate between nerve fiber size (11). Despite conflicting study results, the theory of fiber selectivity remains popular, as it is still unknown why pain transmission is blocked but motor transmission is unimpeded. Likewise, it is unknown whether PRF preferentially alters neurotransmission in unmyelinated C fibers. Although this theory has been suggested, no definitive evidence exists.

Recent studies have examined the effect of electrical fields on upregulation of intermediate early gene (IEG) expression. A current theory is that c-fos proteins, products of IEG expression, are responsible for inducing neuronal changes that modulate pain transmission. A study by Higuchi et al. on dorsal root ganglia (DRG) of rats exposed to PRF at 38°C and RF at 38°C shows that the DRG exposed to PRF had markedly increased c-fos expression in dorsal horn laminae I and II compared to DRG exposed to RF or sham (8). These results imply that c-fos expression is not temperature dependent, but rather is induced by pulsed electrical fields. Whether the increase in c-fos protein is a direct result of electrical stimulation or a secondary post-synaptic effect from activation of DRG has yet to be determined. Other studies, however, have demonstrated conflicting findings. In a recent study conducted by Van Zundert et al., c-fos proteins were measured after rat DRG exposure to sham, RF at 67°C, PRF at 42°C for 120 seconds, and PRF at 42°C for 8 minutes. All treatment groups except for sham showed a significant increase in c-fos proteins in dorsal horn laminae I and II; however, no significant difference was found between RF treated groups and the two PRF groups (12). These results are seemingly consistent with prior evidence that c-fos expression is temperature independent, but do not concur with findings that c-fos is induced by pulsed rather than continuous electrical fields. Although it appears that IEG and c-fos proteins somehow play a role in altering neuronal transmission, further studies are needed.

Ilioinguinal neuralgia can be an unfortunate result of inguinal hernia repair. It can be debilitating for the patient and difficult to treat for the physician. Through early identification of high-risk patients, we were able to treat a majority of our patients with pulsed radiofrequency, with successful results and without the neurodestructive side effects observed with conventional RF. Additional studies both in the clinic and in the lab need to be undertaken in order to elucidate the nature of PRF, so we may better apply this treatment modality in patient care.

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Medical Student Research Day
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Medical student research is now a part of our school's culture. Whereas once students focused on delivering the highest quality of care *currently available* to their patients, many now want to be involved in the development of new treatments for disease. Others, seeing how crucial early diagnosis can be, want to identify novel diagnostic approaches. Still others are interested in health outcomes research to determine the impact of these efforts. Taken together, these young researchers will contribute to easing suffering and improving quality of life for large numbers of people.

In this regard, Mount Sinai again finds itself in the forefront of a large group. Within the last few years, year-long programs to train medical students in how to do research have proliferated, even if there are still too few to satisfy demand. A majority of our students first do research the summer following their first year of medical school, giving them an early view of how clinical medicine and research work together. This helps them decide whether they want to take a scholarly leave during medical school and obtain more in-depth research training. The diversity of student research shows the special opportunities our students have. The quality of the abstracts shows how they avail themselves of them.

These programs would not be possible without the support of Dean Kenneth Davis and Dr. Dennis Charney, Dean for Research. As physician-scientists, they are role models for our students. Dean of Medical Education David Muller is an ardent supporter of the research program and has suggested new ways to broaden it so that students with an even wider variety of interests want to participate. I thank them all for their continued support of medical student research. Grace Oluoch, Administrator, Medical Student Research Office, has worked very hard on the abstract book and to organize today's schedule. Her experience and overview have helped make this day a success. A special thanks to Jairo Munoz, Roberto Alvarez, and Merrill Schindler for developing a mechanism to permit online abstract submission. They saved us countless hours of work. I would also like to thank Annabelle Rinaldo, Associate Director of Student Affairs, for her excellent assistance with organizing Research Day so that it proceeds smoothly. We thank Michelle Sainte, Assistant Dean for Academic Administration, for her continued help and support. Finally, I would like to thank the MSSM Alumni Association for providing medical student research stipends, as well as today's buffet lunch.

Karen Zier, PhD
Associate Dean for Medical Student Research

Comparative Analysis of the Petro-Occipital Fissure in Humans and Rats: Implications for Understanding the Anatomy of Age-Related Hearing Loss. Armand L. Balboni, Joy S. Reidenberg, Andrew D. Bergemann, and Jeffrey T. Laitman. Center for Anatomy and Functional Morphology, and Department of Pathology, Mount Sinai School of Medicine, New York, NY.

The petro-occitpital fissure (POF) lies within a critical interface of cranial base growth and development. The POF of the human skull narrows with age due to an ossification of its soft tissue components. The timing of this closure closely matches the onset of age-related hearing loss (AHL). The POF is closely related to the inner ear, both morphologically and functionally, suggesting that the ossification could be pathogenic for AHL (Balboni et al., 2005). Although of significant importance during growth and development, little attention has been focused on assessing the age related changes to this region. Therefore, this study investigates the POF in both humans and rats in order to assess: 1) the comparative nature of developmental changes, 2) value in age assessment, and 3) potential use as a model system for describing the onset of AHL. Observational analysis was conducted on 14 human cadavers, 73 human crania, and 50 rat crania in order to define and describe developmental changes to the POF. Results in humans and rats show that characteristic changes of POF ossification are present and allow for sorting of crania by age. Our examination of the POF in humans and rats has identified an age related ossification that is temporally unlike other ossifying regions of the cranial base. These findings indicate a basic morphologic similarity of the POF between rats and humans. Given the hard tissue-soft tissue interface within the POF, our data suggest that both biomechanical and molecular forces may influence the mechanism and timing of POF ossification. The further development of an animal model for the aging of the POF will be critical to elucidating the contribution of these processes to pathologies such as AHL.

In Vivo Electrical Propagation in Connexin40 Deficient Atrial Tissue. Baron L. Elvera, David E. Leaf, Cindy Yu, and Gregory E. Morley. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Impulse propagation in cardiac tissue is the result of cell excitability, intercellular coupling, and tissue geometry functioning in concert. Changes in these parameters during cardiac disease may lead to slowing of conduction and an increased risk of cardiac arrhythmias. Cardiac myocytes are connected electrically and metabolically through gap junction channels. Connexin40 (Cx40) and Cx43 are both highly expressed in the adult murine atria, while Cx45 predominates in the sinus node. In the current study, high-resolution optical mapping of voltage dye fluorescence was used on the right (RAA) and left atrial appendages (LAA) of isolated Langendorff-perfused murine hearts. Cx40+/+ (WT) and Cx40-/- 2–4 week old and 4–21 week old mice were studied to assess the effect of reduced Cx40 expression on conduction velocity (CV) at different pacing cycle lengths (100 msec, 60 msec, 30 msec). In the RAA of 2–4 week old mice, a significant increase in propagation velocity was found in Cx40-/- (0.705±0.007 and 0.625±0.006 m/sec at BCL 100 msec; 0.689±0.004 and 0.606± 0.017 m/sec at BCL 60 msec, Cx40-/- (n=4) and WT (n=4), respectively). In the LAA of 2–4 week old mice, however, no significant change in CV was found at all pacing cycle lengths in Cx40-/-. Interestingly, neither the RAA nor the LAA of the 4–21 week old mice showed significant differences in CVs between Cx40-/- (n=10) compared to WT (n=10). In conclusion, optical mapping studies suggest that atrial Cx40 deletion increases electrical propagation velocity in 2–4 week old mice. These data suggest that the relative contribution of Cx40 to conduction in 2–4 week old mice is greater than that in the 4–21 week old mice. This raises an interesting possibility that the coexistence of Cx40 and Cx43 in atrial tissue has a negative effect on cell-to-cell communication and cardiac conduction.

Disclosure of Sexual and Physical Abuse in Adolescents: A Preliminary Assessment of Effective Screening Methodologies. Dominique F. Bayard, Angela Diaz, and Mary Rojas. Division of Adolescent Medicine, Department of Pediatrics, Mount Sinai School of Medicine, New York, NY.

Background: The American Academy of Pediatrics (AAP) recommends routine screening for child maltreatment and abuse. Though recent data suggests that among adolescents, one in five girls (21%) and one in eight boys (13%) report experiencing either physical or sexual abuse, it has also been shown that adolescents do not willingly or spontaneously report past or current victimization events. The methods of face-to-face interview, self-administered questionnaire, and computer interview, have been validated for reporting anxiety and sexual behavior in adolescents. Whether the disclosure of sexual and physical abuse in an adolescent population improves with either of these methods has yet to be established.

Objective: This study will examine different methods for eliciting disclosure of physical and/or sexual abuse experiences, and evaluate the effectiveness of these methods among adolescents.

Methods: Sample: Our study will include a total of 200 adolescent patients aged 12–21 years who are presenting to the Adolescent Health Center (AHC), a comprehensive integrated program of physical health, reproductive health, and mental health. Only patients presenting for an initial history and physical examination will be included. Design: Each subject will be randomly assigned to receive one of four versions of the Childhood Maltreatment Interview Schedule—Short Form (CMIS-SF): (1) Self-administered questionnaire, (2) physician administered questionnaire, (3) Audio Computer-Assisted Interview, or (4) physician-directed inquiry.

Analysis: We will analyze the frequency of abuse disclosure in each screening methodology using a chi-square test to determine if there is an association between disclosure and screening methodology.

Implications: Identifying which interviewing method yields the greatest disclosure is essential to develop and employ standardized, effective, and reliable screening methodology to meet the AAP's recommendation of routine screening for child maltreatment and abuse in adolescents.

Genetic Predisposition of Breast Cancer Patients with ATM Sequence Variance to Adverse Radiotherapy Responses. Hamed B. Lari, David P. Atencio, Jamie A. Cesaretti, Richard G. Stock, Sheryl Green, and Barry S. Rosenstein. Department of Radiation Oncology, Mount Sinai School of Medicine, New York, NY.

This is a case-control multi-center study to identify single-nucleotide changes in the ATM (ataxia telangiectasia mutated) gene that may be associated with increased radiotherapy (RT)-induced morbidity in breast cancer patients. The ATM protein regulates the cell cycle checkpoints and DNA repair in response to the induction of DNA damages by ionizing radiation. This group has previously reported that in a cohort of forty-six breast cancer patients, those who develop late RT reactions are more likely to posses ATM mutations than patients with normal radiation response. The goal of this retrospective study is to elucidate the association of specific polymorphism in ATM and late RT-induced reactions. We have included seventy-seven women who underwent lumpectomy and adjuvant RT. The RT-induced adverse effects are quantified according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer. Blinded to patients' clinical outcome, we have isolated DNA form blood lymphocytes of each patient. Polymerase chain reaction assays were used to amplify each of the coding exons along with short neighboring introns both upstream and downstream of the exons. Utilizing denaturing high-performance liquid chromatography (DHPLC), we have identified specific base pair mismatches, small deletions, or insertions in the aberrant exons in comparison with wild-type ATM gene. Aberrant exons will be sequenced for comprehensive statistical analysis, and the findings will be compared with the clinicopathologic data collected on the study subjects. By elucidating the influence of specific ATM sequence variants causing susceptibility to adverse radiotherapy reactions, future screening for such sequences can be used to predict which patients are most likely to develop complications resulting from radiotherapy. These patients may be encouraged to seek non-radiation treatments for their cancers, or alternatively, may still benefit from radiotherapy, but performed with lower treatment doses.

Spine Density in MAG-Deficient Mice. Lucas Bejar, Devorah Segal, and Patrick Hof. Department of Neuroscience, Mount Sinai School of Medicine, New York, NY.

Gene expression levels of myelin related genes such as MAG, have been shown in gene microarray experiments to be significantly decreased in schizophrenia, which indicates a possible role for dysmyelination in this disease. Many neuropsychiatry disorders have neuronal dysfunction that may be linked to alterations of dendritic spine. To analyze whether spine density is altered by dysmyelination due to loss of the MAG gene, we compared MAG KO and WT animals. We visualized layer III pyramidal cells in the prefrontal cortex of 20–24 month old mice, via intracellular loading with Lucifer Yellow and confocal microscopy. We constructed dendrograms and calculated spine densities. We were able to analyze 2 KO animal and one WT animal. In the two KOs, we analyzed 2 neurons in one animal and 5 in the other. In the WT animal, 3 neurons were evaluated. We analyzed basal and apical dendrites separately. Apical dendrite spine densities were not significantly altered in the KOs. Spine density in basal dendrites was significantly lower in the MAG KO animals ($p = 0.03$, one-sided t test). This data indicates spine density is affected by dysmyelination caused by the lack of the MAG gene. This change in basal spine density may reflect circuit specific pathology affecting certain pathways selectively, and play a role in some of the functional deficits seen in patients with schizophrenia.

The Need for and Attitude towards Counseling Services in Urban Kenya: A Study towards Providing Counseling Services in a Free Community-Based Clinic. Matthew Swan, Kimberly Bowman, Dale Runcie, Ann Ellis, and Gary Rosenberg. Department of Community and Preventative Medicine, Mount Sinai School of Medicine, New York, NY.

Introduction: Studies have demonstrated levels of psychiatric morbidity in sub-Saharan Africa ranging from 10–25% in hospital/clinic patients, levels equal to or exceeding those of the Western world, but with a severe lack of resources to provide care.

Purpose: This study assesses perceptions of counseling, desires for counseling services and the need for counseling as indicated by the presence of anxiety and/or depression in patients visiting a community-based free clinic in Nairobi, Kenya.

Methods: Quantitative surveys were administered in English and Swahili to a convenient sample (N=372) recruited from the RAFIKI Clinic. Participants were aged 18 and over and were predominantly mothers with an average income below $3 (200Ksh) per week. The Hospital Anxiety and Depression Scale (HADS) were used to measure the presence of anxiety and depression. Participants were queried about their interest in counseling services in five categories: depression, anxiety, childcare, family planning, and chronic illness. Patients were deemed to have a strong desire for counseling if they would utilize counseling services at the clinic for at least three of the above categories.

Results: Of the study participants, 88.3% expressed a strong desire for counseling. By HADS criteria 19.6% were depressed and 30.9% had an anxiety disorder. At the time of taking the questionnaire 18% of those with a strong desire for counseling were depressed, as well as 14.8% of those ages 18–30, and 31.3% of participants over 30. Focus groups revealed that participants had not previously used counseling services, but because they valued confidentiality and professional advice, would utilize them if available.

Conclusion: Counseling services are desired by this population and would be utilized if implemented. To further understand how this need may have been affected by population dynamics, a comparative study will be conducted in East Harlem in a population of patients utilizing free community-based clinics.

Polypharmacy in the Elderly: The Patient's View. Ariel C. Bulua, and Beatriz Korc. Brookdale Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, NY.

Polypharmacy is a major cause of morbidity and mortality, particularly in the geriatric population (age ≥ 65). In a study at the Mount Sinai Hospital, patients in a geriatric outpatient practice consumed a mean of 10.48 medications per patient. This is of particular concern because geriatric patients are the most vulnerable to adverse drug reactions and drug-drug interactions. Polypharmacy results in increased admissions to hospitals, non-adherence, and increased costs. Little research has been done to determine how geriatric patients feel about this practice. To this end, we formulated two hypotheses: many people feel they are taking too many medications, and many people are non-adherent. Possible risk factors for these two statements were determined. The study consisted of 100 patient surveys administered one on one in the Coffey Geriatrics Clinic of the Mount Sinai Hospital. Descriptive statistics were applied, including chi square analysis, to calculate the frequencies and percentages of each variable in relation to feelings about medication and compliance. Nearly half of all patients felt they were taking too many medications. This feeling was found to correlate positively with the actual number of medications prescribed, and negatively with both the level of trust in one's doctor and a higher rating of one's health. About 40% of patients admitted to being non-adherent. Non-adherence was found to correlate positively with a higher rating of one's health, and negatively with the level of trust and comfort in one's doctor, and the amount of helpful information offered. In summary, the results showed that a significant number of patients both think they are taking too many medications and are non-adherent. Specifically, people who have a better relationship with their doctor and a better feeling about their health are more likely to feel satisfied with their medications, and more likely to adhere with their drug regimen.

Targeting In Vivo Delivery of siRNAs to Study the Role of KLF6-SV1 in Epithelial Ovarian Cancer. Michelle C. Carley, Analisa Difeo, Goutham Narla, Olga Camacho-Vanegas, and John A. Martignetti. Departments of Human Genetics and Medicine, Mount Sinai School of Medicine, New York, NY.

Epithelial ovarian cancer (EOC), the most lethal of all gynecologic cancers, is the fifth most common cause of cancer death in women. As many ovarian cancers are asymptomatic in early stages, patients often present late in the course of their illness with widespread, disseminated disease. Despite concerted clinical and research efforts, survival rates of patients with late stage EOC have not substantially improved over the last two decades. Therefore, a better understanding of the underlying genetic factors responsible for the initiation, progression, and recurrence of EOC is essential to define novel therapeutic targets and pathways. Our recent studies have identified the tumor suppressor KLF6 and its alternatively spliced isoform, KLF6-SV1 as critical regulators of the development and progression of EOC. Most notably, KLF6-SV1 is over expressed in virtually all late-stage EOC. Cell lines engineered to down regulate KLF6-SV1 exhibit decreased proliferation, invasion, and tumor formation *in vivo*. Therefore, as a starting point for defining a future rational therapeutic strategy, our studies were primarily designed to explore the effect on in vivo tumor growth and behavior of siRNA-mediated treatment targeting KLF6-SV1. State-of-the-art, serum-stable siRNA molecules were designed and tested *in vitro* for their eventual use *in vivo*. Our results clearly demonstrate that siRNA targeted to KLF6-SV1 expression in SKOV-3 cells, a highly aggressive ovarian carcinoma cell line, altered gene expression profiles, markedly decreased cellular proliferation and increased apoptosis. We believe that these results provide ample support for the next phase of these long-term studies: *in vivo* experiments to define the therapeutic potential of siRNA-mediated targeting of KLF6-SV1 in ovarian cancer.

Sexual Health Needs Assessment in Gran Roque, Venezuela. Elliot M. Charen, Elizabeth J. Garland, Philip J. Landrigan, Stephen E. Goldstone, Maria Elena Marin, and Jordana Sosa. Departments of Community and Preventive Medicine, Surgery, and Medicine/Infectious Disease, Mount Sinai School of Medicine, New York, NY, Hospital de Clínicas Caracas, Escuela de Medicina José María Vargas, Venezuela.

Background: Gran Roque Island of the National Park of Los Roques, is located 70 miles from the mainland Venezuela, has a population of 1,400 people, yet over 55,000 tourists visit each year. Tourism has recently introduced HIV to the island. The purpose of this study was to conduct a needs assessment to discover what the extent of the sexual health problem is, what services are in place, what sexual health resources are available to the residents, and whether there is room for improvement.

Methods: Informal conversations took place between the researcher and the residents representing a broad spectrum of occupations including store owners, medical professionals, teachers, government personnel, bartenders, and others.

Results: All residents approached willingly participated in conversations, with 37 discussions greater than 5 minutes. Preliminary results show that there are some developed sexual health services in place on the island, including cheap contraception (birth control pills) and condoms given out free upon request. There exists a basic form of sexual education in the schools, yet the number of sexually transmitted infections (STI's) is high and the age of first sexual intercourse is young. Two major barriers to health care (expensive drugs and medical care) found in the United States are absent on this island. Mision Barrio Adentro, a government sponsored program designed to help underserved communities, removes the first barrier by offering 85% discounts on drugs. The second barrier is avoided because all treatment by the doctor on the island is paid for by the government.

Conclusions: Obstacles to state of the art medical care exist on Los Roques since there is no testing on the island. Addition of Rapid HIV, VDRL tests, and a microscope would improve the care for the population. All the evidence points toward conducting investigations focused on developing educational programs.

Factors Identified by Early-Stage Breast Cancer Patients to Help Cope with Post-Surgical Treatments. Jessica L. Cohen, and Nina Bickell. Department of Health Policy, Mount Sinai School of Medicine, New York, NY.

Breast cancer patients' feedback on their own recent experiences provides the most insight into what factors would increase use and completion of post-surgical treatments. While adjuvant treatments for breast cancer, including radiation, hormonal therapy, or chemotherapy, have been shown to reduce mortality rates by 20–30%, many patients do not complete courses of therapy. Alleviating women's concerns may help them through particularly vulnerable times. The patient population included 20 women with early-stage breast cancer, 6 months after their last definitive surgical breast procedure. Hour long telephone interviews determined the use of efficacious therapies and assessed the women's experiences, knowledge, and beliefs about breast cancer, along with barriers to completing care. Aiming to explore venues that could have helped patients better navigate their adjuvant treatment following surgery, the interviews concluded with an open-ended question asking women to think back over their breast cancer care, and what, if anything, would have improved the process. Qualitative analysis identified 4 common themes: earlier mammograms, insurance, doctors' attitudes, and process of care. Four women wished they had gone in earlier for mammograms; three women identified insurance difficulties, including avoiding expensive medications and needing to buy Medicaid cards for coverage; four women identified issues with doctors' attitudes, especially doctors' ignoring psychological issues of cancer; seven women wished the process of getting care had been easier, specifically regarding difficulties with scheduling/coordinating appointments, long wait times, finding information on the disease and support networks, and poor communication with technicians; six women did not identify any problem areas, which may be due to inability to recall or express concern, rather than an actual lack of suggestions for improvement. Targeting these problem areas with further research focused on interventions during adjuvant treatments may increase completion of post-surgical therapy and improve breast cancer patients' chances for survival.

Autism and the Glutamate System: Potential Pharmacological Treatments. Geoffrey A. Collins, Evdokia Anagnostou, and Eric Hollander. Seaver and New York Autism Center of Excellence, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

Background: Autism spectrum disorders (ASD) are a diverse group comprising behavioral and cognitive variations in which patients notably feature repetitive behaviors/restricted interests as well as impairments in language and social skills. There is strong evidence suggesting that autism is primarily a genetic disorder. Many candidate genes and their protein products pertain to the glutamate system, suggesting that glutamatergic interventions may ameliorate some autistic traits.

Methods: The following database was searched: MEDLINE (1966 to Sept 2003). The following terms were used: glutamate, glutamate receptors, autism, AMPA, kainate, NMDA, metabotropic receptors, GluR2, GluR6, mGlur8, GAD65, amantadine, d-cycloserine, lamotrigine and memantine.

Results: Pathology specimens, genetic screening and imaging studies all suggest that the glutamate system is implicated in autism. Preliminary trials with glutamatergic agents (amantadine, d-cycloserine and lamotrigine) show some effect in reducing certain autistic behaviors.

Conclusions: Based on an understanding of the mechanisms of glutamate signaling, medication trials with other glutamatergic agents, such as memantine, would be of value. Additionally, new research into the function of metabotropic glutamate receptors may provide novel approaches for pharmacological intervention.

Identification of a Novel Tfap2 Co-Factor. Catherine Constable, Cheryl Tan, and Bruce Gelb. Department of Human Genetics, Mount Sinai School of Medicine, New York, NY.

The Tfap2 family of transcription factors has been shown to be associated with heart development. The critical role of Tfap2a in normal neural tube and cardiac development has been demonstrated in mice deficient in this gene. These mice exhibit severe developmental defects, including persistent truncus arteriosus. Also, TFAP2B has been identified as the causative gene for Char Syndrome, which is characterized by familial patent ductus arteriosus. Our lab identified Tfap2d, which differs from other members of the Tfap2 family in protein structure and in expression pattern. While previously identified Tfap2 proteins are specifically expressed in the neural crest, Tfap2d is the only known Tfap2 protein expressed exclusively in the myocardium of the developing heart. To further elucidate the role of this protein, we performed a yeast two-hybrid screen, which yielded several unique candidate interactors, including Ash2L, a chromatin-remodeling protein. This interaction was confirmed by co-immunoprecipitation of tagged proteins in eukaryotic cells. Currently, we are seeking to characterize the nature of this interaction through co-immunoprecipitation assays, first of all to ensure that Tfap2d interacts with endogenous Ash2L and additionally, that the interaction is specific for the Tfap2d protein. We are also using a CAT (chloramphenicol acetyltransferase) reporter assay to determine whether Ash2L is a co-activator of Tfap2d. In this assay, Tfap2d is inserted in a eukaryotic expression vector downstream from the RSV promoter. This plasmid is co-transfected with a CAT reporter containing three tandem copies of the hMtIIa-180 AP-2 binding sequence. The CAT concentration in the presence of Tfap2d is compared with that of controls to determine the level of transactivation.

The Synergistic Immunotoxicity of Benzo[A]Pyrene and Ultraviolet A Impair Langerhans Cell Functions. Jason A. Cordero, Dayuan Gao, Xueyan Zhou, and Huachen Wei. Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

Accumulating evidence indicates that environmental factors contribute to the increasing incidence of skin cancer. Previously our group demonstrated that benzo[a]pyrene (BaP), a ubiquitous pollutant, synergistically increased skin cancer incidence when combined with ultraviolet A (UVA). BaP and UVA significantly depressed contact hypersensitivity and down regulated Langerhans cell (LC) migration induced by fluorescein isothiocyanate, whereas epidermal LC numbers were not altered. These results strongly suggest an impairment of LC function by BaP and UVA. The present study focused on the effect of BaP and UVA on LC functions in vitro. To examine the cytotoxicity, XS106 cells, a murine LC cell line, were incubated with various concentrations of BaP followed by 5 kJ/m2 of UVA. Viability was measured by MTT assay. The lethal dose of BaP was found at 0.312 μM and LD50 was about 0.16 μM. LC migration was assessed by a chemotaxis assay. The BaP plus UVA groups significantly inhibited LC migration induced by CXCL12 in a BaP concentration dependent manner. Together, the cytotoxicity and chemotaxis assay data suggest that synergistically BaP and UVA is toxic to LC and impair the immune system by down regulating LC function.

The Role of Donor TLR2 Signaling in Murine Islet Cell Transplantation. William N. Coward, Jr., Nan Zhang, and Bernd Schroppel. Departments of Medicine/Renal, Gene and Cell Medicine, Mount Sinai School of Medicine, The Recanati/Miller Transplant Institute of Mount Sinai Health. New York, NY.

We hypothesize that the Toll-like receptor 2 (TLR2) recognizes self-derived intrinsic ligands that are present during cellular injury, such as necrotic cells. This signaling mediates proinflammatory responses in early post-transplantation of islets. Murine islets were isolated after collagenase digestion and discontinuous Ficoll centrifugation. To assess the function of TLR2, islets were cultured overnight with or without the specific TLR2 ligand peptidoglycan (PGN) [10 μg/mL]. Additional islets were cultured with or without pancreatic necrotic cells (NC) to simulate conditions present in prolonged islet culture. Marginal mass isografts (n=200 islets) were transplanted under the renal capsule of STZ induced diabetic mice. Islet function was assessed with glucose monitoring and glucose tolerance testing. RESULTS: Screening for TLRs with QPCR reveals that TLR2, TLR3, TLR4, and TLR9 are expressed on isolated islets and on an established ß cell line (ß-TC3). PGN stimulation of islet TLR2 causes a significant increase in MCP-1, TNF-a and IL-6 expression ($p<0.05$). NC co-culture led to similar increases in these proinflammatory mediators. MyD88 and TIRAP, downstream signaling proteins of TLRs, were increased 3.5 fold in the presence of PGN and NC. Reduction in post-transplant blood glucose was significant in control isografts on day 1 and day 2, but not in PGN or NC pretreated isografts ($p<0.05$). Glucose tolerance was impaired in PGN and NC isografts compared to controls.

Conclusions: Murine islets express functional TLR2. Pancreatic necrotic cells are able to stimulate chemokine/cytokine expression similar to the specific TLR2 ligand peptidoglycan. Islet exposure to pancreatic necrotic cells is detrimental to glycemic control by murine islet isografts possibly through TLR2 signaling.

The Quantification of Pericardial Effusion Volume Determined by 2D-Echocardiography Compared to Pericardiocentesis. Christopher L. Cummings, Martin E. Goldman, and Lori B. Croft. Department of Medicine/Cardiology, Mount Sinai School of Medicine, New York, NY.

Background: Pericardial effusion (PE) may develop acutely or chronically over time, reaching relatively large sizes (>1000mL), and perhaps resulting in life threatening pericardial tamponade. 2D-echocardiography (2D-echo) is the most rapid and accurate method to diagnose PE. However, it provides only a semi-quantitative categorization (small<1cm, moderate 1–2cm, or large>2cm) based on the separation of visceral and parietal pericardium. Accurate, noninvasive quantification of PE volume would allow closer monitoring of PE progression and perhaps predict imminent tamponade.

Objective: To compare estimated PE volume using 2D-echo with the volume of fluid drained at pericardiocentesis.

Methods: Patients who underwent pericardiocentesis in the catheterization laboratory were retrospectively analyzed. Inclusion criteria were documented PE volume drained and a 2D-echo within 48 hours prior to drainage. Exclusion criteria were acute PE or poor quality 2D-echo images. The 2D-echos were analyzed by an independent observer who was blinded to the results of pericardiocentesis. PE volumes were calculated in apical 4 chamber, apical 2 chamber, or subxiphoid views using the method of disks. Final estimated PE volume was taken as the average of three measurements. Results: 16 patients with PE drainage volumes ranging from 250–1300mL were analyzed. There was excellent correlation between volumes by 2D-echo and pericardiocentesis: $y = 0.65x + 245$ mL ($r= 0.89$, $P< 0.0001$). Standard error of the estimate=101mL; intraobserver variability=9.5%. Bland-Altman analysis showed a mean difference of −45 ± 150mL. PE volume differed between 2D-echo and pericardiocentesis by an average of 19% (absolute volume difference=125 ± 89mL).

Conclusions: This preliminary study demonstrated that 2D-echo can accurately quantify PE volume compared with the pericardiocentesis volume. Further studies are needed to apply and validate this noninvasive technique in a larger patient population.

Structural Changes in Cortical Bone and Their Role in Fractures of the Distal and Ultra Distal Radius. Gary B. Deutsch, Danielle Casagrande, Richard Ghillani, Roger Levy, and Karl Jepsen. Department of Orthopaedics, Mount Sinai Hospital, New York, NY.

Osteoporosis, characterized by structural weakening of bone and a marked decrease in bone mass, can eventually lead to bone fragility. Non-traumatic fractures of the distal radius, known as Colles' fractures, are often the first manifestation of osteoporosis and indicate that the person has twice the relative risk of developing a hip fracture within fifteen years. Women are four times more likely than men to develop the illness. In previous studies, geometric properties of bone, for example endosteal diameters, perosteal diameters, and moments of inertia, have been correlated with gender, age, and menopausal status. To further define this relationship, thirty-eight cadaver radii were harvested for radiographic and histological investigation. The age and gender of each cadaver was noted. Zero degree AP X-rays were taken of the forearms and digitized for computer analysis. Using the MATLAB program, measurements of the x-rays were obtained, including ulnar variance, cortical thickness, and radial width. For histological examination, cross sections were taken at the thirty percent site of the distal radius and eventually dehydrated and embedded in Caroplastic in order to preserve the fine architecture of the bone. Using a band saw, two millimeter slices were cut from the original cross sections and polished. These thin slides were placed under a microscopic digital camera and high-resolution images were captured for further analysis. The histological coronal images will be studied using Scion Image, allowing us to measure endosteal and perosteal diameters, cortical porosities, and any recognizable resorption spaces. We will use these measurements to determine if significant correlations exist between selected cortical bone properties and age and gender. Recognizing characteristics of cortical bone that become compromised with age may lead to new diagnostic measures that can identify these problems early and new therapies that could target these areas at the onset of osteoporosis to prevent future fractures.

Mutations of Trefoil Factor 1 Prevent Its Tumor Suppressive Activity while Enhancing the Invasiveness of Human Gastric Cancer Cells: An Investigation Guided by Molecular Modeling. Matthew Diamond Xianyang Yio, Jie-yu Zhang, Lu-Hai Wang, Harel Weinstein, and Steven Itzkowitz. Departments of Physiology and Biophysics, Medicine, and Microbiology, Mount Sinai School of Medicine, Weill Medical College o Cornell University. New York, NY.

Trefoil Factor 1 (TFF1) is a key gastric tumor suppressor gene. Like the other members of the TFF family, it is vital for mucosal homeostasis an healing, and it shares the distinct structural fold of the trefoil domain, a three-loop architecture connected by disulfide bonds between six conserved cysteines. TFF1 is unique among the TFFs in that TFF1 knockout mice develop gastric adenomas and carcinomas, and human gastric cancers typically lack TFF1 expression. TFF1 mutations have been found in human gastric cancers and are so far the only naturally occurring mutations reported for any TFF gene. A theoretical estimate of the structural stability of those mutants, as well as comparative studies of related proteins, focused our interest on a surface of the TFF1 Loop 1 edge. Molecular modeling of a number of Loop 1 mutants predicted significant changes to the electrostatic properties of that surface without a disruption of the global fold of the molecule. These computational studies then guided site-directed mutagenesis experiments. Two mutants, A10D and E13K, were found to have lost their ability to inhibit cell growth and block etoposide-induced apoptosis while gaining an ability to promote cancer cell invasion. Although invasion induced by both mutants was blocked by inhibiting PI3-kinase or phospholipase-C, inhibiting ROCK blocked only E13K-induced invasion. This is the first evidence for a functional role of TFF1 mutations in human gastric cancer, demonstrating loss of tumor suppressive activity and gain of cancer cell invasiveness from single point mutations. These studies, the first site-directed mutagenesis experiments of any TFF (other than cysteine substitution), provide the tools to probe both signal transduction mechanisms as well as structural elements responsible for trefoil factor function.

Model for Prediction of Physician Drug Utilization and Cost in Clinical Anesthesia. Ankur M. Doshi, David Wax, Tanuj Palvia, Marina Krol, and David L. Reich. Department of Anesthesiology, Mount Sinai School of Medicine, New York, NY.

Background: Several studies have compared the cost effectiveness of anesthetic agents. While some investigators concluded that anesthetic drug selection significantly affects long-term costs, there are limited data regarding the predictors of more expensive anesthetic agent usage. The purpose of the current investigation was to identify predictors of perioperative anesthetic drug cost.

Methods: An IRB-approved retrospective analysis was performed using 9,823 electronic anesthesia records from cases performed in a six-month period. The total cost of anesthetic and anesthetic adjuvant medications administered by intravenous bolus, intravenous infusion of inhalation was calculated for each case using the hospital formulary price list. Predictors of cost related to the patient, surgical setting, and practitioner were tested. Univariate linear regression was used to identify potential predictors of anesthetic expense per case.

Results: The strongest univariate predictors of anesthetic expense were determined to be anesthetic technique (general anesthesia was most expensive), increasing length of anesthetic, subspecialty of procedure (neurosurgery was most expensive) and patient class (day-of-admission surgery was most expensive), all of which had $r2 >0.05$ and p-values <0.0001. Patient age and weight, American Society of Anesthesiologists (ASA) physical status and nurse anesthetist involvement demonstrated a smaller degree of association, with $0.011<r2<0.05$, but with p-values <0.0001. The lowest degree of statistically significant univariate association was noted with resident involvement, emergency status of procedure, and attending years of experience.

Discussion: Identifying predictors of current usage patterns should help reduce costs by enabling the establishment of benchmarks and ongoing monitoring of expenditures. Modifying the drug selection behavior of outlier practitioners using this methodology may have beneficial effects on anesthetic drug expenditures.

Abdominal Diameter Index and 10-Year Coronary Heart Disease Incidence in Male Bridge and Tunnel Workers in NYC. Adam C. Ehrlich, and Donald A. Smith. Department of Medicine/Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Many studies have shown that increased abdominal adiposity is associated with increased risk of cardiovascular disease. Visceral, or central, obesity produces insulin resistance and hyperinsulinemia which then produces hypertension, increased triglycerides, decreased HDL-cholesterol, and eventually type II diabetes mellitus in genetically susceptible individuals. All of these are risk factors for coronary heart disease, and thus it has been suggested that visceral obesity may be linked to coronary heart disease by this pathway. Recent studies have suggested that the anthropometric measurement of abdominal diameter index, recumbent abdominal height divided by thigh circumference, may be the best measure of central obesity's risk for cardiovascular disease. Telephone interviews were conducted with bridge and tunnel officers in the Triborough Bridge and Tunnel Authority who previously participated in a cross-sectional study in 1993–1994 that examined a multitude of risk factors for predicting prevalent coronary heart disease, including several anthropometric measurements. In that study, abdominal diameter index was the best risk predictor of prevalent coronary heart disease. This follow-up study includes a questionnaire that assesses incident coronary heart disease in the last 10 years in study participants who had no coronary heart disease at that time and who fell into the highest and lowest quartiles of abdominal diameter index. Interviews are still being conducted; thirty-seven subjects (36%) in the lowest quartile and 51 subjects (49%) in the highest quartile have been contacted. No statistical analysis has been done thus far. If there is a significant difference in the ten-year incidence of coronary heart disease in these two groups, it may confirm the hypothesis that abdominal diameter index is the best anthropometric measure of insulin resistance that can be used to predict future cardiovascular disease. This might be useful in large population screenings and underserved communities as a low-cost, quick method of determining cardiovascular risk.

A Restrospective Cohort Study of the Adverse Event Profile of Trimethoprim-Sulfamethoxazole during the First 30 Days following Pediatric and Adult Liver Transplantation. Ann Ellis, Roberto Posada, Sachin Kulkarni, Shirish Huprikar, and Betsy Herold. Departments of Pediatrics and Infectious Diseases, Mount Sinai School of Medicine, New York, NY.

Following liver transplantation, patients are usually placed on Trimethoprim-sulfamethoxasole (TMP-SMX) for PCP prophylaxis. TMP-SMX is considered superior to alternative agents. However, because of hepatic or hematologic adverse events, TMP-SMX is often discontinued soon after transplantation and alternative agents are used, although the causality relationship between the use of TMP-SMX and the occurrence of these events has not been demonstrated. The hypothesis of this study is that the use of TMP-SMX does not result in significantly higher adverse events than alternative agents, and that the abnormalities in liver function and bone marrow parameters are due to confounding factors. The aim of this study is to provide data regarding the incidence of cholestasis or bone marrow suppression following liver transplantation; the timing of these events in relation to the time of transplant, initiation of TMP-SMX, and other confounding variables; how often patients are changed to alternative PCP regimens; and if there are laboratory changes following the switch in PCP prophylaxis. A retrospective cohort study was conducted of liver transplant recipients during the first 30 days following transplantation. One cohort includes subjects in whom TMP-SMX was initiated, subsequently discontinued, and switched to an alternative agent. The other cohort includes subjects in whom TMP-SMX was initiated and not interrupted within the first month following liver transplantation. Trends in liver function, peripheral blood counts, and adverse events were compared in both groups. If it is found that the incidence of adverse events is not higher than that seen with other agents, it could be concluded that these adverse events are not secondary to the use of TMP-SMX. Data from this study will be critical in better understanding whether an association exists between the use of TMP-SMX and the occurrence of adverse events. No studies are currently available that examine this issue in liver transplant recipients.

Indentification of Induction and Supression Signals for Foxp3+ Treg Differentiation. Irene Epelboym, Yaozhong Ding, Jonathan S. Bromberg, and Jonathan S. Bromberg. Department of Gene and Cell Medicine, Mount Sinai School of Medicine, New York, NY.

The cytokine and costimulatory signals that drive or interfere with the differentiation of CD4+ T cells into Foxp3+ regulatory T cells (Tregs) can be precisely defined. Foxp3 is a transcription factor, the expression of which has been demonstrated as being integral to the differentiation and proliferation of CD4+Tcells into CD4+CD25+ Tregs. The specific signals that are activated in the Foxp3+ cells which lead to their differentiation toward the Treg lineage are unknown. Prior studies show that this process is stimulated by TGFb through upregulation of Foxp3, and that it is subject to IL-4-mediated inhibition. It is the focus of this study to determine other input signals that trigger stimulatory or inhibitory effects on the Treg generation. Primary culture of murine CD4+CD25- T lymphocytes was maintained for 3 days in the presence of cytokines and monoclonal antibodies to costimulatory molecules that are known to serve an important function in T cell development and differentiation. These were IFNg, IL-12 (Th1 lineage determinants), IL-4, IL-5, IL-6, IL-10 (Th2 lineage determinants), and anti-CD28, anti-CD2, anti-CTLA4, anti-CD80, anti-CD86, anti-CD40, anti-PD-1 (mAb to costimulatory factors). Expression and transcriptional activation of Foxp3 was quantified using real-time PCR. We found that Foxp3 is induced by TGFb, and that IL-5 and anti-CD28 suppress the TGFb-mediated induction of Foxp3. Tregs are capable of suppressing the inflammatory response in a manner more specific and elegant than immunosuppressive therapy, and they may be an alternative for preventing graft rejection in transplantation. Since Treg proliferation and differentiation can be affected by cytokines secreted by the neighboring Th1 and Th2 cells, it is important to investigate further the signals responsible for modulating Treg response. In our future studies, we will look at time as a factor in TGFb-mediated Foxp3 induction and we will examine how TGFb signaling cascade affects activation of the Foxp3 promotor.

The Production of VEGF and Loss of Anti-tumor Immunity. Steven J. Esses, Christina D. Swenson, and Karen Zier. Department of Medicine/Clinical Immunology, Mount Sinai Medical Center, New York, NY.

Solid tumors, such as the murine fibrosarcoma, CMS5, have developed a variety of mechanisms to evade the immune system, for example, via secretion of inhibitory factors, i.e. VEGF, or the recruitment of cells, i.e. the immature Gr1+/CD11b+ myeloid cells, that suppress immunity. This lab has shown that Gr1+/CD11b+ cells infiltrate the spleens of mice with CMS5 tumors. Mice with small tumors have levels of Gr1+/CD11b+ comparable to naive mice. In contrast, mice with large tumors have increased levels of these cells. Since VEGF can recruit Gr1+/CD11b+ cells from the bone marrow, our goal was to determine whether CMS5 cells secreted this factor. First, we tested whether VEGF was detectable in supernatants of confluent CMS5 cells. We showed that CMS5 cells secreted 2334 pg/ml. To see if VEGF was produced by other tumor cells, three additional lines were tested. All were positive for the factor. In order for VEGF to play a role in immune suppression, it would have to be active in vivo. To test this, mice were inoculated with CMS5 cells and serum was collected from non-tumor-bearing mice, early tumor-bearing mice that still had tumor immunity, and late tumor-bearing mice that had lost anti-tumor immunity, and tested for VEGF. Our findings revealed that, whereas the control and early tumor bearing mice had similar serum levels of VEGF, 77 and 74 pg/ml, respectively, the serum level of late tumor-bearing was substantially greater at 125 pg/ml. Tumor resection has been shown to lead to the return of anti-tumor immunity. Future experiments will examine whether tumor resection leads to a normalization of serum VEGF levels. In conclusion, the tumor CMS5 secretes VEGF, and the production of this factor may play an important role in the loss of anti-tumor immunity.

Changes in Color Vision Following Cataract Surgery. Shlomit Feit Sandler, Julius Shulman, and Scott E. Brodie. Department of Ophthalmology, Mount Sinai School of Medicine, New York, NY.

Background: Artists' color palettes have been known to shift from the blue to the red end of the spectrum as they age. In several well-known cases, this color-shift was reversed, following cataract removal, and sometimes colors in the blue end of the spectrum were enhanced. With age, and especially with cataracts, yellow/brown pigments accumulate in the lens of the eye. It has been argued that the presence of these pigments causes a "filtering effect" on the artist's vision and perception of color, which may account for the change in the artist's color choices. However, this hypothesis fails to account for the similar "filtering effect" on pigments found in the artist's paint itself.

Hypothesis: To account for the artist's altered color palette, we propose that the color palette is a "metameric match" with real-world colors, meaning the human vision process perceives pigments with distinct spectral light distributions as identical colors. Changes in retinal exposure to ultra-violet light following cataract surgery would therefore exaggerate the phenomenon, accounting for enhanced shades following cataract surgery.

Study Design and Methods: We plan to test this hypothesis in subjects who have a cataract in one eye and have had a cataract removed from the other eye: subjects will compare color matches between natural objects and artist pigments. They will undergo standard color vision testing, be asked to match the color of natural objects against standard color samples, and draw flowers from a large palette of colored pencils. Tasks will be performed with each eye separately, under natural and artificial light.

Results. Preliminary results suggest differences in color vision between eyes with and without cataracts through standard color vision testing. Drawings of natural objects demonstrated the use of different colored pencils to depict the same natural hue in indoor and outdoor settings with cataract and non-cataract eyes.

A Comparison of Conditioned Fear Extinction between Patients with Panic Disorder and Normal Controls. Mariel B. Fisher, Jose Martinez, Katherine Nearing, Elizabeth Phelps, and Jack Gorman. Laboratory of Clinical Psychobiology and Department of Psychiatry, Mount Sinai School of Medicine, New York University, New York, NY.

Panic disorder can be explored using fear-conditioning, which involves exposure to a neutral stimulus paired with an aversive unconditioned stimulus (US). The neutral stimulus becomes a conditioned stimulus (CS) after repeated pairings with the US. The CS elicits fear, the conditioned response (CR), in anticipation of the US, a process known as acquisition. These learned associations can fade with repeated exposure to the CS without the US, known as extinction, however they can also be recovered with contextual retrieval cues. The learned associations become pathological when the CS elicits the CR in the absence of the CS/US pairing. In this study, we hypothesize that fear-conditioning will differ among panic patients and healthy controls in the strength of newly acquired conditioned relationships, their tendency to generalize these associations to different contexts, and their ability to extinguish acquired fear. The fear-reinstatement paradigm will be used to study individuals' responses. Subjects will first undergo acquisition and extinction of a CS/US association (blue square image/mild shock) in a particular spatial context. Next, half of the patients and controls will undergo fear-reinstatement (shock alone without blue square) in the same room, whereas the other half will experience reinstatement in a different environment. Skin conductance responses will determine the subjects' intensity of anxiety. Presenting the blue square alone, in the original spatial context as the acquisition and extinction, will test recovery of the fearful response to the blue square. If contextual conditioning does differ between panic disorder patients and normal controls, then we would anticipate seeing altered skin conductance responses during the reinstatement phase of the experiment. Because animal experiments have shown that the contextual portion of fear-conditioning requires hippocampal activation, in another experiment we will use fMRI to compare hippocampal activation during a contextual fear memory task. Both of these experiments are now ongoing.

The Kinetics of Skin Cancer: Progression of an Actinic Keratosis to a Squamous Cell Carcinoma. Aaron E. Fuchs, and Ellen S. Marmur. Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

Actinic Keratoses (AKs) are intraepidermal skin tumors that have the potential to progress to squamous cell carcinomas (SCCs). SCCs are the second most common cancer with more than 200,000 cases in America each year, and many SCCs arise from pre-cancerous AKs. It is estimated that 10% of AKs progress to SCC. The progression from an AK to an SCC is thought to be due to chronic exposure to sun, specifically ultraviolet-B sunlight. This cumulative exposure causes cellular DNA mutations, especially in the p53 tumor suppressor gene. p53 mutations are positively associated with cell proliferation and negatively associated with apoptosis, which subsequently leads to clonal expansion. Understanding the kinetics of this developmental process can help physicians better evaluate, and subsequently treat pre-cancerous AKs. In order to determine the timescale for an AK to progress to an SCC, we examined the clinical histories of all patients diagnosed pathologically with a squamous cell carcinoma between January 1, 2004 and June 30, 2005. Out of a total patient population of 5191, 68 were determined to have had a pathologically confirmed diagnosis of an AK at the same site as the subsequent SCC. The length of time for an AK to progress to an SCC was determined to be 25.56 months (95% CI: 21.03-30.09). While a more controlled in-vivo study is indicated, this data provides a good estimate of the time course from an AK to an SCC. In summary, of the estimated 10% of AKs that will develop into a SCC, the progression will take approximately two years.

Uncovering the Intricacies of Complicated Grief: A Cross-Cultural Prevalence and Risk Factor Analysis. Benjamin E. Goldsmith, R. Sean Morrison, Lauren C. Vanderwerker, and Holly G. Prigerson. Departments of Geriatrics and Medicine, Epidemiology and Public Health, Center for Psycho-oncology and Palliative Care Research, Mount Sinai School of Medicine, New York, NY, Yale University School of Medicine, Harvard Medical School, Boston, MA.

Background: Complicated grief (CG) has been established as a debilitating disorder distinct from classifiable Major Depressive Disorder, Post-Traumatic Stress Disorder, and Anxiety disorders, but little is known about its prevalence and manifestations across racial and ethnic groups.

Objective: To establish the prevalence of CG in white and non-white populations, to identify factors associated with the development of CG, and to compare the prevalence of grief symptoms between these groups.

Design: Secondary analysis of data collected from a study 205 cancer patients and their caregivers (Coping with Cancer, 2002-2004) and 267 caregivers from the Yale Bereavement Study.

Analysis: Multivariate logistic regression was used to identify risk factors associated with CG.

Results: The prevalence of CG was found to vary significantly across ethnic groups. The prevalence of CG was 9.8% in whites, 19% in blacks, 40% in Asians, and 11.1% in Hispanics. CG was found to vary significantly between whites and non-whites 9.8% vs. 22.5% ($p = .029$). Factors associated with the development of CG in multivariate analysis included ethnicity (OR: 3.70, 95% CI: 1.41-9.74) and suddenness of death (OR: 2.87, CI: 1.36-6.07). Non-whites were found to be significantly more likely to report distrust toward others following the death of a loved one (p = .045). There were no other significant differences in CG symptoms.

Conclusions: Our data suggests that non-whites experience CG at a significantly higher rate than white survivors, but that little variation exists in the symptoms of CG grief experienced between whites and non-whites.

The Delivery of Breast Cancer Care by Community-Based Organizations. Julie D. Gribetz, Alicia Cohen, Kruti Shastri, and Nina Bickell. Department of Health Policy, Mount Sinai School of Medicine, New York, NY.

The goal of this project was to assess the ability of community-based patient assistance programs to identify and address the needs of women with early-stage breast cancer who contact and utilize them. Breast cancer is prevalent in today's society. When diagnosed at an early stage, proven effective adjuvant therapies exist. Nevertheless, a percentage of women do not receive these therapies, especially minority women, due to a variety of reasons. Currently, it is unclear whether community based organizations can help reduce that under use by helping overcome barriers to care and by improving women's experiences during the course of cancer treatment. We sought to measure women's satisfaction and overall experiences with community-based organizations. We were able to speak with patients and staff members from 6 community-based organizations that serve women with breast cancer in the New York area. We surveyed 7 staff members and 35 patients who use their services. Patients were interviewed about their initial needs and expectations of the patient-assistance services, how well their needs had been identified and addressed, as well as their overall experiences with the services. Patient satisfaction was assessed and modifying factors such as age, ethnicity, and stage of breast cancer among others, were explored. One staff member from each organization was interviewed in order to compare the program's goals with patients' perceptions of care. We analyzed the data to categorize these needs and identify common themes. This project aims to explore patient experiences and satisfaction with community-based organizations, and in doing so we hope to enable and empower women of different racial backgrounds diagnosed with early stage breast cancer to obtain life prolonging therapies.

Molecular Characterization of Interactions between ERK and Transcription Factor ATF2 in Head and Neck Squamous Cell Carcinoma. Sachin Gupta, and Dianne Duffey. Department of Otolaryngology, Mount Sinai School of Medicine, New York, NY.

This study of head and neck squamous cell carcinoma (HNSCC) examined the role of ERK, an epidermal growth factor receptor (EGFR) pathway protein, in activating transcription factor ATF2. ERK is an important regulator of the G1/S cell cycle progression that when activated, leads to translocation and activation of transcription factors in the nucleus. In HNSCC, EGFR is often over expressed, increasing ERK activity downstream in the EGFR signal cascade. ATF2 has recently been implicated in HNSCC oncogenesis. Support for a potential upstream role of ERK in ATF2 activation comes from studies in other cell lines. By understanding the signaling interactions between ERK and ATF2, gene therapy and additional molecular targeted therapy can be developed for HNSCC. Our hypothesis is that ERK has an upstream role in the regulation of ATF2 in HNSCC. To study effects on cell proliferation and survival, a MTT cell proliferation assay was performed with UM-SCC9 cells and MEK inhibitor U0126 to generate a dose-response curve. Preliminary results suggest that after 48 hours, 25uM U0126 is not toxic to UM-SCC9 cells. To study the relationship between ERK and ATF2 activation in UM-SCC9 cells, western immunoblotting examined the expression of phosphorylated ERK and phosphorylated ATF2 at baseline and following treatment with 10uM MEK inhibitor U0126 for one, six , and twenty-four hours. Preliminary results suggest that the MEK inhibitor inhibits ERK phosphorylation. Results of phosphorylated ATF2 expression following treatment with the MEK inhibitor will be reported. Future studies will examine synergistic or antagonistic effects when the MEK inhibitor and chemotherapeutic agents (i.e., paclitaxel and cisplatinum) are used concomitantly. ATF2 will be inhibited to observe how the MEK inhibitor enhances the cytotoxic effects induced by paclitaxel and cisplatinum. These studies will hopefully give deeper insight into the signaling interactions between ERK and ATF2 and provide additional therapeutic targets for HNSCC.

Is Increased Age a Risk Factor for Emergency Department (ED) Oligoanalgesia? Ben Harris and Ula Hwang. Departments of Emergency Medicine and Geriatrics, Mount Sinai School of Medicine, New York, NY.

Many studies attribute disparities in ED analgesia administration to patient age. Little is known about the quality of ED pain management in older adults. OBJECTIVES: To characterize the differences in ED analgesia between older (>e y.o.) and younger (18 – 64 y.o.) adults presenting to an academic urban ED with painful conditions.

Methods: Patients, â‰¥18 y.o., were prospectively enrolled by reviewing the presenting illness. Study eligibility was based on both chief complaint and final ED diagnosis of conditions requiring analgesic management. Variables collected included: age, gender, triage status, medications administered and prescribed, and times of patient activity (e.g., arrival, assessment, ordering of medication).

Results: From July 1 to July 21, 2005, there were 4,190 ED visits. Of these, 805 patients had conditions with chief complaint and diagnosis warranting pain management: 559 were 18 – 64 y.o., and 101 were >e y.o. A subset of these pati ll injuries was analyzed (ND). Patients >e y.o. (n", mean agevy.o.±10) were compared to patients 18 – 64 y.o. (n", mean ageFy.o.±13). Each group was 77% female. Older patients were more acutely ill by triage score (severity index 3.1±0.6 v. 3.6±0.6, p0.02) and had more fractures (7 v. 2 fractures, p0.06). Older patients had less pain assessment (patients with no pain score at triage: 8 v. 3 patients, p0.04); took longer to get analgesic medication (206 v.93 minutes, p0.07); received less analgesia (patients receiving no analgesia: 9 v. 5 patients, p0.20; NSAIDs: 0 v. 4 patients, p0.04); and were discharged without analgesic prescription: 9/15 patients v. 3/21 patients, p0.004.

Conclusion: In this study, older adults received less analgesia and less pain assessment for similar conditions than younger and less acutely ill adults. Future studies will include more patients with a broader range of presentations and diagnoses and additional analyses f analgesia.

STI Risk Assessment in Gran Roque Island, Venezuela. Jonathan S. Hausmann, Elizabeth J. Garland, Philip J. Landrigan, Stephen E. Goldstone, Maria Elena Marin, and Jordana Sosa. Departments of Community and Preventive Medicine, Surgery, and Medicine/Infectious Diseases. Mount Sinai School of Medicine, New York, NY, Ambulatorio Dr. Tulio Villalobos, Los Roques, Hospital de Clinicas Caracas, Escuela de Medicina Jose Maria Vargas, Venezuela.

Background: Gran Roque Island (GRI) is the major inhabited island in Los Roques National Park, Venezuela, with 1,400 residents. Tourism brings 55,000 people to the island every year, and along with it, the possibility of introducing infectious diseases. The purpose of this study was to assess the risk of sexually transmitted infections (STI) in the community and implement plans for treatment, prevention, and education.

Methods: Out of 721 eligible adults, 103 permanent residents of GRI, aged 18 – 49, were randomly chosen from a 2004 census list. Of these, 74 enrolled in the study; the other 29 were unavailable. An anonymous, confidential, validated questionnaire based on the HIV/AIDS/STD Behavioral Surveillance Survey was administered in Spanish to participants. Two out of four HIV positive residents were also informally interviewed.

Results: Most adults were not married but lived with a sexual partner, and although they did not use condoms with their partner, they could name several places on the island where they could obtain them. Everybody had heard of STIs, but only a handful could correctly name any symptoms. Some young men reported having sex with female tourists, and this source of transmission was responsible for infecting one man, and later his wife, with HIV. Educational and condom distribution sessions were conducted on the island. Plans were made with the government to conduct blood tests for HIV, hepatitis, and syphilis to all willing residents in September 2005.

Conclusions: The high flux of people on the island and the lack of knowledge about STIs combine to make the incidence of STIs on Gran Roque Island particularly alarming. Of concern is the potential under-reporting of information on sensitive subjects in a survey that was not self-administered. Future efforts should focus on increasing awareness of STIs, especially on recognizing symptoms and promoting health-seeking behaviors.

Infra-Red Coagulation for the Treatment of High-Grade Anal Displasia in HIV-Negative Men Who Have Sex with Men. Joshua S. Hundert, and Stephen Goldstone. Department of Surgery, Mount Sinai School of Medicine, New York, NY.

Research Question: Is the IRC (Infra-Red Coagulator) more effective at preventing recurrences and progression to cancer of anal HSILs in HIV-negative MSM than it is in HIV-positive MSM.

Background and Methods: We performed a retrospective chart review on HIV-negative MSM treated for HSIL treated with the IRC.

Patients were screened with anal cytology and standard anoscopy. Those with abnormal findings underwent High Resolution Anoscopy (HRA), in which biopsies were taken. If biopsies returned as HSIL, patients were offered IRC ablation of those dysplastic areas. All patients had at least 6 months follow-up. Patients were surveyed to see if lesions had been cured, persisted, or if new (metachronous) lesions developed. Persistent and metachronous lesions were treated with IRC.

Results: 68 patients met enrollment criteria. Mean patient age was 39.6 years. 143 lesions were treated. The mean number of lesions per patient was 2.2. The length of follow-up ranged from 150 days to 1618 days, with an average of 753. 100 lesions were treated on the first IRC treatment. The average number of lesions at first treatment was 1.5. 27 patients underwent a second IRC treatment. 19 patients (28%) had persistence of their primary lesion at or after their 6-month post-treatment follow-up visit. 34 patients (52%) developed at least one new lesion in a different location. In the study HIV-positive subjects, the percentage of patients with persistent lesions was the same as in this study (28%). However, the percentage of patients that reported new lesions was lower in the HIV-negative population (52%) than in the HIV-positive population (65%).

Conclusions: IRC is a safe, ambulatory, effective treatment for anal HSILs with minimal associated morbidity. Our data suggests that IRC is as effective, if not more so, for treatment of anal HSIL in HIV-negative subjects as it is in HIV-positives.

Xenobiotic Phenols in Early Pregnancy Amniotic Fluid. Stephanie M. Engel, Brynn Levy, Zhisong Liu, Dana M. Kaplan, and Mary S. Wolff. Departments of Community and Preventive Medicine, Human Genetics, Pediatrics, and Ob/Gyn. Mount Sinai School of Medicine and Tris Pharma Inc., New York, NY.

Hormonally active chemicals, such as bisphenol A (BPA) and phytoestrogens, have been detected in amniotic fluid. Phytoestrogens and BPA are weak hormone agonists. Phytoestrogens also possess anti-estrogenic activity possibly by competitive binding to the estrogen receptors, and can reduce genotoxic damage to cells by antioxidant and other mechanisms. They can also inhibit cellular growth and proliferation by inhibiting tyrosine kinase cell-signaling activity and by down regulating certain membrane receptors (e.g. erbB2, EGFR). Consequently, concern has been mounting that prenatal exposure to hormonally active agents may result in reproductive or neurological effects. We examined the concentration of three phytoestrogens (enterolactone, daidzein and genistein) and BPA in residual amniotic fluid samples that had been collected early in pregnancy from a population of women in the United States. We found detectable levels of enterolactone, daidzein, genisten and BPA in 21 residual amniotic fluid specimens that were collected before 20 weeks gestation. Samples were obtained by amniocentesis from women who were referred to the Mount Sinai Medical Center because of advanced maternal age. Phytoestrogens were present in higher concentrations than BPA. Enterolactone was detected at the highest concentration (median 95.9 ug/L), followed by daidzein and genistein (9.5 and 1.4 ug/L, respectively). BPA was present at very low concentrations (10% > LOD of 0.5 ug/L). The relative concentration of the chemicals measured in amniotic fluid were identical to those in urine reported by other studies, i.e., enterolactone > daidzein > genistein >> BPA. Amniotic fluid is a source of fetal exposure to polar xenobiotics that come from the mother. The results of this analysis are described in an upcoming article in Reproductive Toxicology: Stephanie M. Engel, Brynn Levy, Zhisong Liu, Dana Kaplan, Mary S. Wolff, "Xenobiotic Phenols in Early Pregnancy Amniotic Fluid." In press. Volume 21:1. Reproductive Toxicology.

The Photoprotective Efficacy of Genistein in Human Skin. Anna I. Kirkorian, Julian O. Moore, Stephanie Diamantis, Mark G. Lebwohl, and Huachen Wei. Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

Skin cancer is the most common cancer in the United States with an estimated incidence of one million new cases in 2004. The most important environmental factor in the development of skin cancer is exposure to UV irradiation resulting in DNA damage. Genistein, the most abundant isoflavone of the soy derived phytoestrogen compounds, has been previously shown to have antiphotocarcinogenic properties. These include the capacity for scavenging reactive oxygen species, inhibiting DNA damage, and down regulating UVB-induced signal transduction cascades associated with carcinogenesis. Genistein is also a potent antioxidant and an inhibitor of tyrosine kinase. The aim of our study is to investigate the photo protective efficacy of genistein in vivo in human skin, in response to acute doses of UVB. Dorsal skin samples from twenty-eight healthy human subjects, Fitzpatrick skin types I through IV, were pre-treated with both genistein and a vehicle control prior to exposure to UVB radiation equivalent to one minimal erythemal dose (MED). Punch biopsies were obtained and the cyclobutane pyrimidine dimer (CPD) profiles were assessed via immunohistochemical analysis of paraffin-embedded skin specimens. CPD represents the primary DNA lesion induced by exposure to UV irradiation. A preponderance of such lesions results in the mutation of critical genes implicated in carcinogenesis. Genistein inhibited the immunoreactivity expression profile for UV-induced DNA damage as evidenced by the decreased formation of CPDs in the genistein-treated samples when compared to the vehicle-treated skin. Our results represent the first characterization of the photo protective effect of genistein against UV-induced DNA damage in vivo in human skin. These results serve to further validate our conclusion that genistein may serve as a potent chemo preventive agent against photocarcinogensis.

Doubletime Affects Wingless Signaling and Planar Cell Polarity by Regulating Dishevelled Signal Specificity. Thomas J. Klein, Andreas Jenny, and Marek Mlodzik. Department of MCDB, Mount Sinai School of Medicine, New York, NY.

Canonical Wnt/Frizzled (Wnt/Fz) and non-canonical Frizzled/Planar Cell Polarity (Fz/PCP) signaling networks regulate a vast array of biological processes, from cell growth and division to tissue polarity and differentiation. Mutations of several signaling molecules in these pathways have been associated with a number of human diseases, including lung, breast, colon, and prostate cancer. Thus, identifying factors that regulate these two related pathways is of importance to the understanding of both development and disease. Several molecules, including the transmembrane receptor Frizzled and the cytoplasmic protein Dishevelled (Dsh), have been shown to signal to both pathways. The mechanism by which these factors selectively signal to one pathway versus the other is poorly understood. Upon stimulation by either pathway, Dsh becomes hyperphosphorylated, an event that is important for downstream signaling events and may impart signal specificity. A number of kinases have been identified that can both bind to and phosphorylate Dsh, including Casein Kinase I epsilon (CKIe). Xenopus studies and cell culture experiments have shown that CKIe affects both canonical and non-canonical signaling. Here we report that double-time (dbt; a.k.a. discs overgrown, dco), which encodes the Drosophila CKIe homolog, is important for both Wnt/Fz and Fz/PCP signaling. Using loss-of-function studies in the fly eye and wing, we demonstrate that dbt is necessary for both pathways. Using over expression studies, we show that dbt is sufficient to induce Wnt/Fz and Fz/PCP phenotypes in these tissues. Genetic interactions supported by biochemical data demonstrate that dbt promotes Wnt/Fz signaling while inhibiting Fz/PCP.

PTTG1, a Novel Repressed Target of KLF6 Tumor Suppressor—a New Pathway of Carcinogenesis? Ursula Lang, Sigal Kremer-Tal, Goutham Narla, Andrew Paris, Steven Yea, and Scott L. Friedman. Department of Medicine/Liver Diseases, Mount Sinai School of Medicine, New York, NY.

Background: KLF6, a Krüppel-like transcription factor, is a tumor suppressor dysregulated in a number of human cancers. While p21 is a key transcriptional target, many other downstream targets of KLF6 are unknown. Microarray analysis of a KLF6 +/- and KLF6 +/+ mouse livers was used to uncover new KLF6-regulated genes. Of these, the most differentially induced (~2-fold) in KLF6+/- mice was the pituitary tumor transforming gene (PTTG1). PTTG1 inhibits sister chromatid separation, and drives malignant transformation; its over expression disrupts cell division, generates chromosomal instability, leading to further mutations. The aim of our study was to validate microarray data by quantitative real-time PCR (QRT-PCR). We analyzed liver and prostate tissues from KLF6 +/+ mice and KLF6 +/- littermates. We also analyzed hepatocellular carcinoma (HCC) patient samples and cell lines stably expressing KLF6 to validate the correlation between KLF6 and PTTG1 mRNA levels. Results: By QRT-PCR, KLF6 mRNA was reduced by > 80% in 14 KLF6 +/- mouse livers compared with 10 KLF6 +/+ livers, which correlated with a mean 1.2 fold increase in PTTG1 mRNA in KLF6 +/- animals. In prostates from these same KLF6 +/- mice, KLF6 mRNA was reduced ~50%, with a 2-fold increase in PTTG1 mRNA. In 12/19 patient samples there was a mean ~70% decrease in KLF6 mRNA and 2-fold increase in PTTG1 mRNA. In HepG2 hepatoblastoma cells, stable infection with KLF6 retrovirus increased KLF6 mRNA 15-fold, associated with a 40% decrease in PTTG1 mRNA. In Huh7, a HCC cell line, stable infection with KLF6 retrovirus led to a ~1.8 fold increase in KLF6 mRNA and 25% decrease in PTTG1 mRNA. Conclusion: An inverse relationship between KLF6 and PTTG1 suggests that PTTG1 may represent a transcriptionally repressed target of KLF6. Thus, inactivation of KLF6 in human cancer may lead to dysregulated PTTG1 and contribute to tumorigenesis.

Development of an International Maternal-Child Health Education Program for Mothers in New York City and Santa Cruz, Bolivia. Alexandra P. Leader and Andrea Rothenberg. Department of Health Education, Mount Sinai School of Medicine, New York, NY.

The purpose of the project was to develop an adaptable maternal-child health curriculum for distinct communities that are historically underserved and disadvantaged. The project involved two phases. In the first phase, we synthesized the information and skills garnered through participating in a local community health initiative in order to prepare a comprehensive and versatile health education curriculum for pregnant women, new mothers and infants living in a local, underserved and disadvantaged community. As translator, facilitator and co-instructor for the Prenatal Care and Assistance Program at Mount Sinai-Queens, a program that prepares pregnant women for labor and delivery and provides instruction and guidance for early parenting and infant care, we developed a curriculum that aims to merge clinical and educational aspects of mother-child health for mothers living in the community of Long Island City, New York. The curriculum constitutes an educational module that is adaptable to meet the specific needs of pregnant women who are ready for labor and delivery and lack adequate health services. The second phase of the project involved taking the curriculum to mothers and infants living in Santa Cruz, Bolivia, a community that shares the basic social, economic and health characteristics of our target community in New York. We worked to formally identify the specific, recognized needs of pregnant women and infants in Santa Cruz so as to focus this health education module accordingly. The curriculum was utilized to teach a six-week program of prenatal health classes in five different clinical and non-clinical settings throughout the city of Santa Cruz and we are currently analyzing our data to evaluate the efficacy of the curriculum in providing pregnant women and infants of Santa Cruz with the knowledge, skills and resources to support a healthy pregnancy and transition into early parenting.

Multimarker Molecular Detection of Metastasis in Pathologically Negative Lymph Nodes from Melanoma Patients. Diana P. Leon, Cristina Mangas, Josep M. Hilari, Ferrandiz Carlos, Cindy Yueh, Liqiang Xi, and Tony E. Godfrey. Departments of Medicine/Hematology/Oncology, and Dermatology. Mount Sinai School of Medicine, New York, NY, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain.

Sentinel lymph node (SLN) status is the most important factor in melanoma staging and patient prognosis. Prognosis for lymph node-negative subjects (AJCC Stages I and II) should be very good, but unfortunately up to 20% of these patients suffer disease recurrence. One possible explanation for this is the presence of occult metastatic disease that is undetected by routine pathology. Previous studies have shown that molecular analysis of SLN increases the sensitivity of lymph node metastasis detection in individuals with node-negative melanoma but at the cost of specificity. We hypothesized that a multimarker Real Time quantitative PCR assay would maintain the high sensitivity of previous studies but improve specificity and therefore provide more accurate prognostic information. We obtained 370 dissected lymph nodes from 195 patients who underwent SLN biopsy at the HUGTiP in Barcelona. All nodes were tumor-negative by standard histopathological and immunohistochemical techniques. Half of each node was stored frozen and RNA was isolated. Quantitative RT-PCR was used to quantify the expression of the melanoma-associated mRNAs MART-1, Tyrosinase, SSX-2, MAGE-A3, GALNaC and PAX-3. Sensitivity and Specificity of these markers for predicting recurrence were examined using ROC curves. QRT-PCR results were compared with disease recurrence to determine clinical relevance. Median patient follow-up was 49 months and 11 of the 195 patients recurred. Kaplan-Meier survival estimates did not show significant differences in survival based on individual markers or marker combinations. Quantification of mRNA should increase the specificity of SLN staging by decreasing the number of false positive results. However, we found that specificity was still a problem and that not all recurrences were identified by the markers. Marker positivity was not significantly correlated with recurrence. However, the frequency of recurrence in this data set was low compared with other studies and our study may be underpowered despite having a large sample size.

Fluorophotometry to Evaluate the Cornea in Patients Utilizing CRT to Correct Myopia. Huma Naikoo, Bernard Tinio, Chakravarthy Koonapareddy, Michael Ahdoot, Tony Leung, Shmuel Mahgarefteh, and Penny A. Asbell. Department of Ophthalmology, Mount Sinai School of Medicine.

Corneal Refractive Therapy (CRT) is a non-surgical procedure that reduces myopia by reshaping the cornea to allow light to focus properly. An FDA clinical study has shown CRT to be a safe, reversible, and effective method to correct low to moderate myopia. Since CRT utilizes rigid gas permeable contact lenses to mold the corneal shape from prolate to oblate, this study will test the health and integrity of the corneal epithelium. Our hypothesis is that CRT will have no damaging effects on the epithelium. This study employs fluorophotometry, a technique documented to be safe and highly sensitive, to evaluate corneal barrier function, an indicator of epithelial health. 0.5% fluorescein eye drops are placed in each patient's eyes, and the amount of fluorescein that seeps into the cornea is quantified with a fluorophotometry camera. Corneal epithelium health is inversely proportional to the amount of fluorescein absorbed. Baseline measurements will be taken prior to CRT fitting, and follow-up measurements with the patients will take place 1 day, 1 week, 1 month, and 3 months after the fittings. Statistical analysis of these measurements will determine the effects of CRT on the health of the corneal epithelium. Preliminary results have shown that the fluorescence of control eyes, which have not undergone CRT, remains stable and is reproducible among patient populations. If the final results show that CRT does not significantly alter fluorescence, and thus have limited damage to the corneal epithelium, then this treatment can be confidently recommended to short-sighted patients as a new alternative to refractive surgery and other conventional corrective options such as eyeglasses and contact lenses.

The Efficacy of Antenatal Corticosteroids between 32 and 34 Weeks in Patients with Preterm Premature Rupture of Membranes. Heather I. Levin, Enrique Soto, Thomas Musci, Natali Aziz, Yvonne W. Cheng, Andrea Weintraub, Errol Norwitz, Keith Eddleman, Joanne L. Stone, Aaron B. Caughey, and Larry Rand. Departments of Obstetrics and Gynecology, Mount Sinai School of Medicine, California Pacific Medical Center, University of California, San Francisco, Yale University.

Objective: Administration of antenatal corticosteroid (ACS) to women with preterm premature rupture of membranes (PPROM) at 32–34 weeks gestation is controversial. Authorities debate the theoretical risk of infection against the unclear benefit at that gestational age, despite the high prevalence of respiratory distress syndrome (RDS). Our aim is to evaluate risks and/or benefits of ACS administration to patients with PPROM between 32 and 34 weeks gestation.

Study Design: A retrospective cohort study of patients at three teaching institutions with PPROM at 32–34 weeks between 1993–2005 was conducted. Those who received ACS were compared to those who did not. A course of ACS was defined as receiving =24 hours of steroids prior to delivery. Patients were excluded if they had a prior course of ACS, a fetal anomaly, or chorioamnionitis on admission. The primary outcome variable was a reduction in the incidence of neonatal RDS, powered to detect a 50% decrease. Secondary outcomes included chorioamnionitis, neonatal sepsis, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and hyperbilirubinemia.

Results: Of 856 patients with PPROM at 32–34 weeks who met inclusion criteria, 500 (58%) received ACS and 356 (42%) did not. Patients who received ACS at 32-0/7 to 32-6/7 weeks had a 44% reduction in RDS compared to those who did not (OR, 0.50; 95% CI, 0.31–0.81). At 33-0/7 to 33-6/7 weeks there was no significant difference. There were no statistically significant differences in any of the secondary outcomes at either gestational age.

Conclusion: There is benefit without apparent risk to the administration of ACS at 32 weeks gestation in patients with PPROM. No such benefit was demonstrated after 33 weeks. This should serve as the basis for a prospective randomized controlled trial looking at the effect of giving ACS between 32–34 weeks in PPROM.

Association of Traditional Cardiovascular Risk Factors and Coronary Calcification in Elderly Japanese-American Men: The Honolulu Heart Program. Sandy C. Liang, Kamal Masaki, Randi Chen, Bradley Willcox, Alvin Ikeda, Katsuhiko Yano, J. David Curb, and Robert Abbott. Division of Biostatistics and Epidemiology. Brookdale Department of Geriatrics & Adult Development, Department of Geriatric Medicine, Mount Sinai School of Medicine, New York, John A. Burns School of Medicine, University of Hawaii, Pacific Health Research Institute, Honolulu, Hawaii, Kuakini Medical Center, Honolulu, Hawaii, University of Virginia.

Background: Coronary artery calcification (CAC) as assessed by multisplice computed tomography (MSCT) has been proposed as a noninvasive method to assess coronary artery disease. While studies have shown relationships between traditional risk factors for cardiovascular disease (CVD) and CAC, there were no studies done in the elderly. This report examines the associations between CVD risk factors and CAC in a population of very old Japanese-American men.

Methods: The Honolulu Heart Program is a longitudinal cohort study initiated in 1965 to study CVD in Japanese-American men in Hawaii. From 2004 to 2005, MSCT was performed to assess CAC in 222 men ages 84 to 96 years (mean age=87). CVD risk factors were available from examinations given 12 years prior to scanning.

Results: After adjusting for age, prevalence of diabetes increased significantly by CAC quartiles (14.4% in the first quartile to 25.4% in the fourth quartile, p=0.059). There was also a significant positive relationship between CAC quartiles and fasting glucose (p=0.03), pack-years of cigarette smoking (p=0.02), and physical activity index (p=0.01). Other traditional risk factors showed positive associations with CAC quartiles, but statistical power was limited by a small sample size.

Conclusions: This study in very old Japanese-American men shows that diabetes, fasting glucose, pack-years of cigarette smoking, and physical activity index are significantly associated with CAC. These findings are consistent with the observation that effects of CVD risk factors, particularly diabetes, persist in the very old. It remains to be determined whether CAC has the potential to predict CVD events in extreme old age.

The Effect of Hemi-Sync Music on Intra-operative Stress Reduction in Patients Having Awake-Surgery for Parkinson's Disease or Dystonia. Michelle M. Liao, Irene P. Osborn, David C. Kramer, Francis B. Sullivan, and Ron L. Alterman. Departments of Anesthesiology and Neurosurgery, Mount Sinai School of Medicine, New York, NY.

The goal of this study is to determine whether Hemispheric Synchronization (Hemi-Sync) music will reduce intra-operative anxiety in patients undergoing deep brain stimulation (DBS). DBS is a surgical procedure that is used to treat neurological symptoms of Parkinson's disease and dystonia, such as tremor, rigidity and walking difficulty. During this procedure, patients are kept awake and unsedated with their heads pinned and fixed into a frame. While local anesthetic is administered, general sedation is not allowed because patients must be conscious for the assessment of neural and motor function. Therefore, patients undergoing the DBS procedure often experience increased baseline anxiety, which poses a significant challenge in maintaining blood pressures below the safe limit of 140 mmHg. Hemi-Sync is a binaural beat music designed specifically to induce brain-wave states that promote relaxation. Thus, we hope to determine whether listening to Hemi-Sync intra-operatively can improve patients' well-being during awake-surgery. Patients will be randomly assigned to one of two groups. For 10 minutes intra-operatively, patients will receive either 1) Hemi-Sync through noise-canceling headphones or 2) noise-canceling headphones alone. Patients will take a State-Trait Anxiety Inventory questionnaire before and after this 10-minute period to assess anxiety. Blood pressure, heart rate, bispectral index, and pharmacologic regulation of blood pressure will also be recorded. Group differences pre-intervention and post-intervention will be analyzed. Through this study, we hope to determine whether the use of Hemi-Sync represents a novel non-pharmacologic alternative that provides comfort and sedation for patients during awake-surgery.

Establishing Normative Data for the Anatomic Localization of Memory Strategies and Emotional Response to Musical Stimuli of Differing Emotional Value: 3TESLA F-MRI Analysis of Classically-Trained Musicians. Wen Lin, Cheuk Y. Tang, Jin Fan, and Thomas P. Naidich. Departments of Radiology and Psychiatry, Mount Sinai School of Medicine, New York, NY.

Rationale: (1) Musicians with "absolute pitch" (AP) use associative memory to immediately identify the pitch of any tone or tone pair. Musicians with "relative pitch" (RP) use working memory to identify the relationship between any pair of tones (the interval), but cannot identify the precise pitch of either. (2) Specific tone pairs and chords carry distinct emotional values.

Hypotheses: (1) Presentation of single tones, tone pairs, and chords to classically-trained musicians, who differ only in the way they process pitch (AP vs. RP), will disclose the site(s) of working memory for tonality. (2) Presentation of tone pairs and chords with differing emotional "valence" (harmonious vs. dissonant intervals; major vs. minor chords) will disclose the sites activated by the musicians' appreciation of these different emotional valences.

Materials and Methods: The investigators will recruit 20 classically-trained musicians, (10 AP and 10 RP) who are native English speakers matched for age, gender, and the tonality of their parental languages. Musical stimuli will be presented visually ("silent hearing") by marking keys on a projected piano keyboard to ensure uniformity of the stimuli presented despite the noisy MRI environment. Event-related, blood oxygen dependent (BOLD) three Tesla functional magnetic resonance imaging (f-MRI) (Siemens, Erlangen Germany) will be used to assess the cerebrovascular responses of these musicians' brains as they perceive the individual tones, tone pairs and chords. General linear modeling (GLM) and statistical parametric mapping (SPM) of the f-MRI datasets from each participant will be used to identify the anatomic sites of tonal and emotional processing.

Results: Pending. IRB approval of the project has been received. GCRC funding has been approved conditional upon clarification and amplification of specific queries. Initial data and conclusions are expected by late Fall 2005.

Development of a Surgical Implant to Prevent Laryngopharyngeal Reflux by Increasing Resistance to Retrograde Flow at the Level of the Upper Esophageal Sphincter. Michael J. Lipan, Joy S. Reidenberg, and Jeffrey T. Laitman. Center for Anatomy and Functional Morphology, Mount Sinai School of Medicine, New York, NY.

Background: Laryngopharyngeal reflux (LPR) is a manifestation of symptoms and signs resulting from abnormal exposure of the laryngeal and pharyngeal mucosa to gastric secretions refluxing through the upper esophageal sphincter (UES). Medical treatment failures, and patients with life-threatening conditions associated with reflux, are being increasingly treated with anti-reflux surgery involving fundoplication at the lower esophageal sphincter. In contrast, surgical intervention at the UES has not been attempted. The objective of this study is to determine the efficacy of a retropharyngeal implant at the UES to augment the anti-reflux properties of this barrier.

Methods: Cadaveric heads (n=3) were harvested and the distal end of the proximal esophagus was tied over a catheter for water infusion. The retropharyngeal space at the level of the UES was exposed to allow insertion of implants. Implants were made of silicone rubber in various widths and either cylinders (diameters: 0.6, 0.8, 0.9cm) or half-cylinders (radii: 0.3, 0.45, 0.6cm) in shape. Maximal intraesophageal pressure was measured with a water manometer during water infusion using no implant and then using each successively larger implant in place.

Results: Using no implant resulted in the lowest maximal pressure (21.7 cm H2O). Increasing width of the implant correlated with increasing maximal pressure (range 46-117 cm H2O). The only exception to this trend was that the half-cylindrical implant of 0.6cm width had a higher pressure than a cylindrical implant of 0.8cm width (76 vs. 69 cm H2O respectively).

Conclusions: Increased resistance to liquid flow past the level of the UES can be achieved using any of the implants tested. Increased resistance correlated with increased width of the implant for those of the same shape. Half-cylindrical implants achieved greater resistance than cylindrical implants of the same width. The initial success of this method shows promise for future development of an implant for patients with LPR.

Airway Management of Acromegalic Patients: A Retrospective Study. Joyce C. Lo, Irene Osborn, and David Kramer. Department of Anesthesiology, Mount Sinai School of Medicine, New York, NY.

Acromegaly is an endocrine disorder in adults that is caused by an adenoma of the pituitary gland that secretes excess growth hormone (GH). Excess GH produces serious systemic changes such as organomegaly, diabetes, cardiovascular disease, and hypertension, and untreated, will lead to a shortened lifespan. Thus, treatment is essential in acromegalic patients, typically with transsphenoidal resection of the pituitary gland. Other morphologic changes, such as prognathism, soft tissue overgrowth (including pharynx, tongue, lips, epiglottis, and larynx), and recurrent laryngeal nerve dysfunction, alter the airway. These alterations may be associated with airway obstruction, difficulty in ventilation, and obscured visualization of the larynx during laryngoscopy, which increase the difficulty of securing an anesthetic airway. To provide these patients with optimal care, it is important to determine the preferred method of airway management. Therefore, in this study, we characterized the methods used in airway management of approximately 200 acromegalic patients and the specific success rates of each of these methods by conducting a retrospective study that spanned a 13-year period and evaluated over 1000 patients aged 18-65 who underwent pituitary surgery. In particular, we compared the technique used for intubation, the number of intubation attempts required for success, determined failure rates, and reviewed complications to airway management, including airway trauma. Intubation methods compared include traditional direct laryngoscopy, fiberoptic intubation (asleep and awake), glidescope, intuabating laryngeal mask airway, and surgical airway. We believe that our data will indicate that while acromegalic patients may pose more challenging airway management issues, current methods and devices available allow for safe and proper management of these patients. Furthermore, our patient pool is larger than any study previously published on the acromegalic airway, and, therefore, we believe that our results will provide important information on optimal airway techniques to utilize in the management of acromegalic patients.

The Effects of Jasmonic Acid and Methyl Jasmonic Acid on Melanoma Metastasis. Margarita S. Lolis, Yongyin Wang, and Huachen Wei. Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

Melanoma is currently the fastest growing of all cancers and has a strong tendency to metastasize to the brain, liver, lungs, and bone. The prognosis of metastatic melanoma is poor, with a median survival time of 7 months and limited treatment options. Jasmonic acid (JA), a growth inhibitor produced ubiquitously in plants, may be effective in the inhibition of tumor metastases. The purpose of this study is to determine whether jasmonic acid (JA) and its methyl ester, methyl jasmonic acid (MJ) decrease the rate of metastasis of melanoma cells *in vitro*. The antimetastatic effects of JA and MJ were evaluated on the migration and invasion of a highly metastatic B16F10 melanoma cell line. Toxicity assays, dose response and temporal response experiments were performed to determine the effects of JA and MJ. Migration and invasion assays were designed using filters that were precoated with fibronectin and/or matrigel (reconstituted basement membrane) and incubated with 105 B16F10 cells with or without JA and MJ. JA and MJ were found to significantly inhibit the migration of B16F10 melanoma cells into extracellular matrix components and their invasion into reconstituted basement membrane (matrigel). Since JA is a known protease inhibitor, its ability to inhibit migration and invasion of melanoma cells may be modulated by hydrolyzing aminopeptidases in tumor cells. This *in vitro* data suggests that JA and MJ may be able to inhibit tumor cell migration and invasion possibly through a mechanism involving aminopeptidase inhibition in tumor cells. Future experiments aimed at elucidating the mechanism of action of JA/MJ, such as an aminopeptidase assay, will be performed.

Determination of the Causes of Ocular Toxicity Secondary to the Prostaglandin Ocular Hypotensive Analogues. Edward I. Marcus, Michael Ahdoot, Seth P. Epstein, and Penny Asbell. Department of Ophthalmology, Mount Sinai School of Medicine, New York, NY.

Purpose: To test whether toxicity of prostaglandin ocular hypotensive analogues (POHA) are secondary to the preservative, not the active agent.

Background: Glaucoma is usually treated with POHAs. To date, there is no direct comparison of the ocular surface toxicity of the different POHAs or whether the observed toxicity is due to the active ingredients or the preservatives used.

Methods: Toxic agents will proportionately reduce the conversion of MTT viable dye to formazan crystals by corneal epithelial cells (CEPI 17) and conjunctival cells (P61 Clone). Formazan is quantified by absorbance at 570nm. Ninety-six groups of latanoprost, bimatoprost, travoprost and unoprostone in concentrations of 0.001% to 1%, with and without the preservatives benzalkonium chloride, benzododecinium bromide, sodium perborate, and stabilized oxychlorocomplex in concentrations of 0.01% to 0.10% will be examined. Media alone and 10% formalin will be utilized as controls. Seven to ten wells per group will ensure reproducibility/statistical significance. Cells will be seeded at 1×10^3 cells/well in 96 well tissue culture plates with 200 μL of suitable media. When confluent, after decanting, 100 μL of the appropriate test solution will be added. After 1 hour and decanting the solution, 150 μL of MTT will be added for 4 hours. After decanting, the precipitate will be dissolved by 100 μL of acid isopropanol and the absorbance of each determined.

Conclusion: Preservatives proved to exhibit the majority of the toxicity exhibited by the commercial POHAs: bimatoprost > latanoprost > travoprost.

Significance: Patient compliance is of utmost importance for successful glaucoma therapy. Determining the relative toxicities of the antiglaucomatous agents should enable physicians to maximize compliance by selectively prescribing the least toxic agent.

ERM Proteins Regulate Axon Guidance. C. David Mintz, Ioana Carcea, Meghann Burke, Daniel McNickle, Stephen Salton, and Deanna L. Benson. Fishberg Department of Neuroscience, Mount Sinai School of Medicine, New York, NY.

The establishment of functional connectivity during brain development requires that growing axons follow an elaborate set of extracellular chemotactic cues that serve as an addressing system for appropriate synaptic targets. Numerous guidance cues and their transmembrane receptors have been identified, but the system which mediates the complex intracellular response of the growth cone remains unelucidated. We asked whether the ERMs, a highly homologous family of membrane-cytoskeletal linker proteins that have been implicated in cellular motility, are involved in axon guidance. Using well characterized dominant negative and constitutively active ERM mutants and an in situ axon guidance assay conducted in developing rat neocortical brain slices, we demonstrate that intact ERM function is required for appropriate axon targeting. In the slice guidance assay appropriate axon trajectory is known to be dependent on the guidance cue Semaphorin 3A and its receptor, Neuropilin-1. We show that C-terminal threonine phosphorylation of the ERMs, which tightly regulates their activity, is responsive to extracellular application of Semaphorin 3A. Furthermore, we demonstrate that ERMs regulate the endocytosis of L1, a transmembrane protein that determines the plasma membrane expression of Neuropilin-1. These results identify ERMs as a new class of regulators of axon guidance. Additionally, they allow us to construct a model in which ERMs play a pivotal role in regulating cellular adaptation to guidance cues, a phenomenon that has been widely described, but not adequately explained at a molecular level.

Quantitative Evaluation of CNS Neuronal Loss Secondary to Glaucoma in DBA/2 Mice Using MRI and Correlation with Histological Evaluation. Steven Naymagon, Melissa Kujawski, Patrick Hof, Cheuk Tang, Thom Mittag, and John Danias. Departments of Ophthalmology, Neurobiology and Radiology, Mount Sinai School of Medicine, New York, NY.

Background: Glaucoma is a group of diseases in which optic nerve degeneration can lead to impairment or vision loss. The loss of optic nerve axons is followed by the loss of retinal ganglion cells (RGC). There also appears to be neuron loss in the central nervous system (CNS) targets of RGCs. This relationship has been documented for the human disease but not for the DBA/2 mouse, a rodent glaucoma model that develops high intraocular pressure and RGC death starting around 12 months of age.

Purpose: To study the relationship between the death of RGCs and loss of CNS neurons in a mouse model of glaucoma. To investigate whether magnetic resonance (MR) imaging can be used as a non-invasive method for quantifying glaucomatous neuronal loss in the CNS.

Methods: Young (pre-pathologic) and aged (glaucomatous) DBA/2 mice were perfused under anesthesia with 4% paraformaldehyde. Their brains were removed and further fixed in the same solution. MR imaging of the brains was performed in a 9.4T magnet with a custom coil. The brains were cryopreserved in 30% sucrose and sectioned with a cryostat. Serial sections through the colliculi were Nissl stained. MR images and histological sections were analyzed to determine the volume of the superior and inferior colliculi using stereological methods. The ratio of superior/inferior colliculus volume (CVR) was used to determine differences between young and aged DBA/2 animals.

Results: CVR mean(+SD) in aged animals as determined by histological analysis were 1.46(+0.22) and 1.44(+0.21) for right and left colliculi respectively ($p>0.05$). MR image analysis as well as comparison of CVRs of young and aged mice is ongoing.

Conclusions: No significant differences were detected between left and right colliculi in this group of aged DBA/2 mice. Evaluation of MR imaging as a means of non-invasive measurement of neuronal loss secondary to glaucoma is ongoing.

The Effect of Massive Operative Transfusions on Liver Transplant Outcome. Greg J. McKenna, Eunice Hahn, Peter J. Neuburger, Sander S. Florman, Gabriel E. Gondolesi, Sason Roayaie, Charles M. Miller, Myron E. Schwartz, and Sukru Emre. Baylor University Transplant Institute, Medical School, Recanati/Miller Transplant Institute. Baylor University Medical Center, Mount Sinai School of Medicine, Tulane University, Cleveland Clinic, Mount Sinai Hospital, New York, NY.

Introduction: Usually unfavorable, massive operative transfusions in liver transplant (OLT) recipients may be beneficial given a transfusions immunosuppressive nature and the effect of a de facto total plasma exchange on HBV/HCV viral loads. We examined OLT recipients with operative of >50U PRBC.

Material and Methods: We studied OLT recipients from 06/89-07/03 to find those with operative transfusions of >50U PRBC, analyzing demographics, complications, rejections, outcomes and postop HCV/HBV viral loads.

Results: 70 (48 M, mean age 50.3y, mean donor age 43.3y) of 1890 OLT recipients were transfused>50U PRBC (mean 73.6 PRBC). Early mortality was high, with 30d patient and graft survival of 57.1% and 47.1% respectively. Factors associated with massive transfusions include marginal donors (64%), previous surgery (37%), re-OLT (24%) and iatrogenic injury (7%). Re-OLT specifically for HCV had no impact (15.7% survived >30d vs 15.6% <30d). Complications were high (PNF 14%, HAT 7%, sepsis 47.9%, cardiac/MI 24%, ARDS 18.3%, re-op 31%). For >30d survivors, the 1, 3, 5-yr patient and graft survival was 97%, 88%, 71% and 97%, 84%, 67% respectively, exceeding overall 1,3,5-yr patient and graft survival for all OLTx patients (83%, 78%, 69% and 73%, 67%, 58% respectively). The incidence of transplant specific infection was 6.6%, biliary complications 6.6%, acute rejection 36% (mean 1.7 episodes). 100%

(8/8) of HBV+ and 36% (4/11) of HCV+ >30d survivors had undetectable viral loads at the latest clinical visit.

Conclusions: After massive transfusion many OLTx recipients die in the first 30d from complications (i.e. sepsis, ARDS, MI). However, the outcome of those that survive 30d are optimal with excellent graft and patient survival rates, low rejection rates and clearance of HBV and HCV in many recipients.

Barriers to Lead Screening in East Harlem and Bushwick. Rachel E. Outterson, Nathan Graber, Deborah Vasquez, Maida Galvez, Vinay K. Aakalu, and Ray Cornbill. Department of Community and Preventive Medicine, Mount Sinai Medical Center, New York, NY.

Lead damages the developing brain. Manifestations include decreased intelligence and an increase in behavioral problems. Though the incidence of lead poisoning has declined in recent years, it is still a very real problem in some New York City (NYC) neighborhoods. Crucial in the prevention of lead poisoning are the screening and education provided by well-child health care providers. Doctors in NYC are legally required to test the blood lead level (BLL) of children at 1 and 2 years of age, assess lead exposure risk by questioning until the age of 6 and obtain a BLL on any child without a previous documented BLL if they are receiving Medicaid benefits. In 2002, only 72% of children in NYC had even one BLL screening by the age of 2. In the Bushwick and East Harlem neighborhoods the rates were only 60%. Our aim in this study has been to identify barriers to universal screening for exposure to lead. We created a 30-question, self-administered survey for pediatric health care providers in East Harlem and Bushwick. Using lists compiled by the Citywide Immunization Registry, we located, contacted and distributed surveys to these practitioners. The survey addresses knowledge, belief and practice as they pertain to risk factors, services to prevent and manage lead poisoning, screening, treatment and perceived barriers. As of August 5, 2005, we have collected data from 37 out of 60 practitioners who received surveys in East Harlem and 35 out of 50 in Bushwick. We expect to continue collecting from both neighborhoods and to accrue sufficient data to represent the vast majority of practitioners in these neighborhoods, offering a generalizable data set. This information will enable us to design interventions to overcome the identified barriers.

Genetic Variability in the Morphology and Cellular Content of the Periosteum. Nirnimesh C. Pandey, Christopher Price, and Karl J. Jepsen. Leni and Peter W. May Department of Orthopaedics, Mount Sinai School of Medicine, New York, NY.

The periosteum is an organ that covers bone and is composed of a condensed fibrous tissue and a neurovascular network of osteogenic and fibroblastic cells. Osteogenic stimulation of the periosteal surface can potentially increase the strength and antifracture efficacy of long bones better than current agents that target endosteal and trabecular cells. Advances in understanding the nature of the periosteum can thus be of immediate use in fighting degenerative bone disease, osteoporosis, osteomalacia and periostitis. Because periosteal growth through various stages of mammalian life has a later impact on bone strength, we undertook a comparative morphological study of periosteal growth for three genetically distinct strains of inbred mice. The inbred strains, A/J, BL/6J and C3H, were examined because they exhibit unique cortical bone geometries and molecular content as previously studied by the lab. We tested the hypothesis that variability in adult bone properties are derived in part from variability in the function of the periosteum. Femurs with intact periosteum were harvested at two age intervals and administered vital tetracycline labels to study cellular kinetics. Mice were examined at 32 days, during the greatest rate of outer surface bone growth, and 63 days, during the slowing of growth. We sectioned and stained the femurs for each genotype (n=10/strain/age), and tested for variation in specific morphologic and cellular traits of the periosteum, including cell layer thickness, vascularity, regions of osteoclastogenesis, and osteogenic vs. bone reabsorbing areas along the length of the femur. Based on continued analysis, we expect to see strain- and age-specific variability in the aforementioned traits.

The KLF6 Tumor Suppressor Regulates Expression of GADD45γ, a Cell Cycle Regulatory Protein, In Vivo and In Vitro. Andrew J. Paris, Sigal Tal-Kremer, Goutham Narla, Steven Yea, Ursula Lang, Rachel Schwartz, and Scott L. Friedman. Department of Medicine/Liver Diseases, Mount Sinai School of Medicine, New York, NY.

Hypothesis: KLF6 regulates GADD45γ expression in vivo and in cultured tumor cells.

Background: The KLF6 tumor suppressor is a transcription factor whose activity has been linked to activation of p21 and interaction with cyclin D1. GADD45γ is a growth suppressor, induced by DNA damage, which activates MTK1 causing G2/M arrest and apoptosis by increasing p38/JNK activity. GADD45γ was identified as a possible KLF6-regulated gene as its expression by cDNA microarray was decreased in tissues from KLF6 +/- mice compared to KLF6+/+ littermates. Specifically, in KLF6 +/- liver samples there was a 51% reduction of GADD45γ expression and a good correlation (R=.62) between GADD45γ and KLF6 mRNAs. Since KLF6 is dysregulated in 87% of human hepatocellular carcinoma (HCC), we compared GADD45γ mRNA expression in 18 HCC tumors to surrounding non-tumor tissue. We also extended our studies to PC3M cells, a metastatic prostate cancer cell line, by evaluating the impact of KLF6 downregulation on GADD45γ mRNA following stable expression of KLF6 si-RNA.

Results: By real time PCR and immunoblot, KLF6 mRNA and protein were significantly decreased in KLF6 +/- livers relative to the wt littermates: average KLF6 ($p=0.05$) and GADD45γ mRNAs ($p=0.001$) were decreased 85% (n=24 mice) in the KLF6 +/- livers. Similar results were obtained in the prostate and stomach. In 18 HCC patient samples, 89% (16/18) had decreased KLF6 mRNA expression and 72.2% (13/18) of tumors had decreased GADD45γ expression relative to surrounding tissue. On average, HCC tumors expressed 70% less GADD45γ ($p=0.02$). In PC3M cells, stable expression of KLF6 si-RNA reduced KLF6 mRNA by 75% and GADD45γ by 50%.

Conclusions: This data suggests a novel role for KLF6 in regulating GADD45γ expression. Future studies will employ promoter deletion analysis and ChIP to investigate GADD45γ as a direct transcriptional target of KLF6.

High Molecular Weight Seminal Plasma Proteins Interfere with the Anti-HSV Activity of Candidate Topical Microbicides in Clinical Development. Sarju S. Patel, Marla Keller, Ehsan Fam, Kathleen Hogarty, Natalia Chesenko, Cindy Goldberg, Ana Tuyama, Josephina Carlucci, and Betsy Herold. Department of Pediatrics and Infectious Diseases, Mount Sinai School of Medicine, New York, NY.

Background: HSV infection increases the risk of HIV acquisition, and co-infection with HIV and HSV increases both HIV transmission and replication. As these epidemics continue to expand, novel preventative strategies are urgently needed. This study evaluates three candidate topical microbicides, pharmacologic compounds designed for vaginal application to prevent acquisition and transmission of HIV and HSV. By binding viral glycoproteins, these compounds inhibit infection in cell culture, explants, and animal models. While these compounds retain their activity in cervicovaginal secretions, no studies have assessed activity in the presence of seminal plasma. The purpose of these studies is to test the anti-viral activity of candidate microbicides in seminal plasma.

Methods: Clinical specimens were obtained from consenting, healthy individuals, ages 18-50. HSV plaque assays were performed on human cervical epithelial cells. Microbicides evaluated include PRO 2000, a sulfonated napthalene compound currently in large-scale Phase II/III trials; SAMMA, a non-sulfonated anion; and SpM8CHAS, a sulfonated amphiphilic umbrella compound. Cells were pre-treated for 1 hour at 37°C with one of the drugs diluted in PBS or cervicovaginal lavage fluid (CVL). HSV-2 isolates were then introduced in PBS, seminal plasma, or a control HEPES buffer adjusted to the pH and total protein concentration of seminal plasma. The cells were again incubated for 1 h at 37°C. Infection was monitored by counting plaques at 48 h. Results: Seminal plasma significantly interferes with anti-HSV activity of all three compounds and reduces the intrinsic anti-viral activity of CVL fluid. Fractionation studies using Centricon preps suggest that the interfering proteins are of higher molecular weight (>100kD). Mass spectrophotometry studies to identify the mediator(s) are ongoing.

Conclusion: Seminal fluid reduces the effectiveness of anionic microbicides in cell culture. If validated in ongoing clinical trials, identifying the protein(s) and mechanism of action should facilitate development of new formulations to overcome this phenomenon.

Comparative Morphological Study of Tendon-Bone Insertions. Jason S. Pruzansky, Damien M. Laudier, Vincent M. Wang, Mitchell B. Schaffler, and Evan L. Flatow. Department of Orthopaedic Surgery, Mount Sinai School of Medicine, New York, NY.

Tendon failure at its insertion into bone is a common and debilitating orthopedic injury, yet relatively little is known regarding the relationship between tendon morphology and function. Furthermore, different tendons have been shown clinically to have differing susceptibilities to damage. The aim of the current project is to compare the anatomy and morphology of normal rat patellar, Achilles, and supraspinatus tendon-bone insertions. Rat tendons were harvested fresh immediately following animal sacrifice and processed for light microscopic histological examination. To characterize potential differences among tendons, collagen fiber network, cellular phenotype and density, and fibrocartilaginous dimensions will be quantified. Preliminary data has suggested distinct anatomic variants among the three different insertion sites. Among the tendons examined, the thickness of calcified fibrocartilage varies widely in shape and thickness, as does the quantity of non-calcified fibrocartilage. The cellularity noticeably changes between insertion sites and the morphometry of the tidemark differs as well. Additional samples are presently being processed for further analysis. By analyzing the morphometry of insertion sites qualitatively and quantitatively we hope to find a relationship to functional properties, which may provide insight into the etiology of clinical tendon pathologies. This research on normal tendons will also provide a foundation for future analyses of the morphologic alterations due to damage or injury.

Effect of Community-Based Asthma Education Programs on the Asthma Outcomes of Inner-City Children: A Literature Review. Taisha Y. Roman and Carl Johnson. Departments of Ambulatory Pediatrics and Medical Education, Mount Sinai School of Medicine, New York, NY.

Introduction: Asthma is the most common chronic childhood disease in the United States. Health care disparities exist for minority children with asthma. In recent years, enormous efforts have been implemented to reduce gaps in asthma care. Community-based asthma education is one intervention that aims to educate parents and children on the self-management of asthma using familiar community settings. However, despite such efforts, asthma continues to be a leading cause for child hospitalizations in poor inner-city neighborhoods such as East Harlem.

Objectives: To determine the extent of community-based asthma education programs for children in inner cities. Community-based asthma education is defined as educational programs NOT performed in the hospital setting. A critical review of the literature sought to determine: 1.The extent of community-based asthma education programs for children in inner cities, 2.The effectiveness of these programs, and 3. The limitations of community-based asthma education programs. Methods: A Medline search was conducted using the key word terms ‘asthma education programs’ and ‘community-based,’ for publications from 1995-present.

Results: 12 articles relevant to community-based asthma education were reviewed. Of these, 4 studies (in St. Louis, Harlem, West Philadelphia and Boston) assessed the effectiveness of community-based asthma education programs for inner-city youth. Common outcome measures were asthma control and the frequency of Emergency Department visits. Each study concluded that asthma education has a positive affect on asthma care.

Conclusions: Despite inner-city communities having some of the highest prevalence and hospitalization rates of asthma, there are few publications about community-based asthma education programs. This finding may play a role in asthma health care disparities for children from inner-city communities. Future interventions should focus on the implementation of effective community-based asthma education programs that use uniform and proven asthma outcome measures and should consider collaborations with parents and children living with asthma.

Cost-Effectiveness of Probiotic Treatment in Preventing Hospital-Aquired Clostridium Difficile-Associated Diarrhea. Allyson L. Rovetto, Cheuk Yin Lai, and Henry Sacks. Department of Community and Preventive Medicine, Mount Sinai School of Medicine New York, NY.

Hypothesis: Prophylactic treatment with the probiotic saccharomyces boulardii, a live, non-pathogenic yeast, is cost-effective in preventing antibiotic-associated diarrhea (AAD) in hospitalized patients.

Background: AAD occurs in 5-30% of hospitalized patients given antibiotics; the most worrisome is that caused by clostridium difficile (CDAD), which can cause toxic megacolon and death. A recent study gave a conservative cost estimate (not including doctors' costs nor post-hospital care costs) for CDAD of $1.1 billion per year in the US. Increasing antibiotic resistance and recurrence rates indicate a need for a cost-effective preventive therapy. There is growing evidence that probiotics such as s. boulardii can prevent AAD and recurrent CDAD.

Results: Base-case estimates and ranges: Probability of AAD, given antibiotics 20% (5-30%); effectiveness of s. boulardii in preventing AAD 63% (48%-74%); increase in hospital costs $3669 per patient with AAD; probability of relapse of AAD 20% (5-45%), mortality of CDAD 1% (0.5-4%). Major adverse events from s. boulardii, primarily bloodstream infections (BSI), appear rare but increasing, although firm estimates are lacking. For a course of s. boulardii costing less than $50 per patient, the model yielded an average cost saving of $712 per patient. The most likely to benefit were patients over age 65 and those hospitalized longer than 2 weeks. Sensitivity analyses showed that preventive treatment with s. boulardii will save lives, unless BSI occur in more than 4/1000 treated patients, which seems unlikely.

Conclusion: In hospitalized patients being started on antibiotics, simultaneous administration of s. boulardii can reduce costs by over $700 per patient and probably save lives. Better data are needed on the rates of severe adverse events due to s. boulardii, but appear highly unlikely to outweigh the benefits.

Needs Assessment of Women's Health Issues in Delhi, India Conducted with Peer Educators. Shonali Saha, Kasturi Gupta, Suneel Vatsayan, and Henry Sacks. Departments of Medical Education, Sociology, Community and Preventative Medicine, Mount Sinai School of Medicine, New York, NY, Maxwell School of Syracuse University, Nada India Foundation.

The purpose of this study was to conduct a three-fold assessment of the needs of the women of Chattarpur by partnering with the non-profit Nada India Foundation. The study recommends programming strategies for women's health in Chattarpur, an “urban village” in South Delhi. The 10-week community needs assessment had three components: (1) What do female community members' perceive their health needs to be? (2) What are the medically determined needs? (3) What are the observed needs from a third party perspective? Researchers partnered with women of the community to train them in health related data collection,formulate a research agenda, and carry out the study, which aims to determine whether community participation improves the quality and impact of health related research. Women acted as peer educators and researchers, interviewing over fifty community members regarding health related issues. Peer educators reported findings in a weekly focus group. Appreciative inquiry was used in interviews and focus groups. Local doctors were interviewed to determine medical needs and identify discrepancies between their views and those of community members. The principle investigator lived in the community to gain a third party perspective. Preliminary findings indicate that health care services and basic necessities are inadequate for women living in Chattarpur. Women interviewed felt they lacked proper health information and wished available diagnostic and treatment services were expanded. Doctors agreed that services needed expanding but did not deem it necessary to provide any information because they consider most women in the community incapable of understanding it. In response to these findings, Nada India Foundation will continue to train peer educators in health related topics to conduct outreach that will educate women and connect them to care. Findings will be shared with community members, local health care providers, the research community, and government agencies.

PTSD and Adherence to Treatment in HIV Patients. Mary Ann Cohen, Jeffrey Weiss, Anupana Reddy, Erin Samuels, and Jack Gorman. Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

The present study is an examination of the relationship between Post-Traumatic Stress Disorder and nonadherence to treatment among patients with HIV. Successful HIV treatment requires a high degree of adherence, which includes taking at least 95% of scheduled HAART doses, as well as attending a multitude of regular and time consuming medical appointments. It is therefore crucial for both doctors and patients to recognize and understand PTSD and its potential impact on adherence.

Methods: 352 patient charts were non-systematically selected from the charts of the 1005 patients referred for psychiatric consultation by their primary HIV physicians between 1998 and 2003 and were then coded. In order to examine the associations with adherence, the medical charts of 62 of the 352 persons were reviewed for adherence data, such as number of scheduled medical appointments attended, CD 4 count and viral load in the one-year period post-psychiatric consultation.

Results: While the results in this small sample do not reach significance [chi-square=1.9, p=0.295], there was a higher percentage of nonadherence in patients with PTSD (67%) than in patients without PTSD (42%). These preliminary findings suggest a trend such that in the larger sample of 1005 patients these differences would achieve significance, and further studies are thus warranted. If we further break the groups down into both PTSD and substance abuse (n=9, 78% non-adherent), PTSD alone (n=3, 33% nonadherent), substance use alone (n=17, 53% nonadherent), neither diagnosis (n=9, 22% nonadherent) the finding becomes somewhat more significant (p=0.114) and points in the direction of comorbid PTSD and substance abuse being the strongest risk factor for nonadherence, suggesting this more specific question as an important area of future investigation in its own right.

The Incidence of Iatrogenic Splenic Injury in Laparoscopic versus Open Colectomy: A Comparison Study during the Ten-Year History of Laparoscopic Colectomy at The Mount Sinai Medical Center. Adam L. Sandler, Marcus Malek, and L. Brian Katz. Department of Surgery, Mount Sinai School of Medicine, New York, NY.

Background: Iatrogenic splenic injury necessitating splenectomy is a well-recognized, and potentially serious, complication of colon resection. Iatrogenic splenectomy is associated with significant morbidity and mortality, including bleeding and the Post-Splenectomy Sepsis Syndrome, which results from increased susceptibility to encapsulated organisms. Our study aims to compare the incidence of iatrogenic splenic injury in laparoscopic colon resection with that of open colon resection over a ten-year period at Mount Sinai.

Hypothesis: An initial review of medical records and spleen specimens analyzed by the Department of Pathology suggests a higher incidence of iatrogenic splenectomy during open colon resections. We hypothesize that, controlling for other factors, including the larger volume of open procedures, the higher incidence among patients undergoing the open procedure is due to its more invasive nature as compared to the laparoscopic approach.

Study Methods and Design: We conducted a retrospective chart review of all the medical records of Mount Sinai patients who underwent colectomy in the last ten years. The goal was to identify those who suffered iatrogenic splenic injury as a result of the procedure. Confirmatory evidence of splenic injury was garnered from pathology reports of splenic injury following colon surgery. Finally, we hope to relate our findings to the relevant clinical literature on iatrogenic splenic injury.

Results/Significance: As a result of our review, we found twelve cases of iatrogenic splenectomy occurring during open colectomy and none during laparoscopic colectomy. The indication for colon resection in the patients who suffered iatrogenic splenic injury included colon adenocarcinoma, ischemic bowel, familial adenomatous polyposis, and diverticulitis. Laparoscopy, in general, has many well-recognized advantages over open procedures, including post-operative recovery time and length of stay. This retrospective review of our experience at Mount Sinai presents yet another potential advantage of laparoscopy during colon resection.

Association of Surgical Education Database. Celia M. Divino, Scott Q. Nguyen, Luke R. Scalcione, and Linda P. Zhang. Department of General Surgery, Mount Sinai School of Medicine, New York, NY.

Purpose: Propose an adjunct to conventional surgical education for medical students and surgical residents.

Background: The Association of Surgical Education (ASE) plans to pilot a database composed of various surgical topics. A gamut of surgical topics are represented in PowerPoint format. These power points will aid in the education of surgical residents and medical students. Senior residents, chief residents, or attending faculty may access specific surgical topics via the ASE website (http://www.surgicaleducation.com/). All power points are downloadable Microsoft PPT formatted files. The PowerPoint presentation may be used as basis for discussion or formal lecture.

Methods: The construct of the database is based on uniformity and systematic presentation of surgical material. Uniformity is maintained via skeleton power points—this assures continuity from presentation to presentation. All database power points have been standardized including background, clinical presentation of information, charts, etc. Each PowerPoint presents surgical cases in clinical vignette style. The case presentation challenges the student/resident to think clinically and propose a logical management and work-up of a simulated patient.

Results: Included is a list of completed presentations: Incidental Adrenal Mass: Rebecca Evangelista, MD Jaundice: Hilary Sanfey Inguinal Hernia: Karen Brasel, MD, MPH Abdominal Pain: Barry Mann, MD; Philip Wolfson, MD Intussusception: Philip Wolfson, MD Care: Kimberly Ephgrave, MD, FACS Acute Mesenteric Ischemia: Scott Q. Nguyen, MD; Celia M. Divino, MD Pulmonary Embolus: Linda P Zhang; Scott Q. Nguyen, MD; Celia M. Divino, MD Tension Pneumothorax: Luke R Scalcione; Scott Q. Nguyen, MD; Celia M. Divino, MD.

Conclusions: The preliminary compilation of PowerPoint presentations is promising. Various contributors from several medical academic institutions have complete pilot PowerPoint presentations. The database is slated for trial in the near future. A component of the database will allow for revision/comments regarding power points.

Investigating Parents' Knowledge of Pediatric Environmental Health Issues. Melissa L. Schapiro, and Leo Trasande. Departments of Pediatrics, and Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY.

Exposure to environmental pollutants is linked to a number of pediatric health problems, including asthma, allergies, and learning disorders. Parents who are unaware that pollutants can harm children are unlikely to take steps to protect their children from exposure, so it is important to ascertain parents' knowledge. Our goal is to study parents' concerns about pollutants, as well as their understanding of the potential effects these pollutants can have on their children's health. We will visit pediatric clinics in two neighborhoods, one with low SES and one with high SES, to administer a questionnaire to 100 parents of children ages 2–12 years. We will compare the responses of parents living in the low and high SES neighborhoods, as well as the responses of parents whose children do and do not suffer from the various health problems commonly linked to pollutant exposure. We hypothesize that most parents do not understand some of the connections between pollutants and children's health. This study is intended to enable us to make recommendations for future community education campaigns on children's health issues. Additionally, we believe findings from this study may provide new information for local government officials to better understand community members' concerns about pollution and its impact on children's health.

Pilot Study of the Use of Intravenous Immunoglobulin in HIV-Associated Myelopathy. Lauren D. Schiff, Katia Cikurel, David Dorfman, and David Simpson. Departments of Neurology and Psychiatry, Mount Sinai School of Medicine, New York, NY.

HIV-associated myelopathy is characterized by white matter vacuolization predominantly of the posterior and lateral columns of the thoracic spinal cord. It is the most common cause of spinal cord disease in HIV/AIDS; however there is no effective treatment currently known. Although the etiology of HIV-myelopathy is unknown, it shares similarities with HTLV-1-associated myelopathy which has been shown to improve with intravenous immunoglobulin (IVIg). Based on this evidence we sought to evaluate the safety and efficacy of IVIg treatment in patients with HIV-associated myelopathy. Seventeen patients with HIV-associated myelopathy received 2 daily infusions of IVIg twice over a 56-day study period, on days 1–2 and 29–30. Patients were evaluated at baseline and at days 14, 28, and 56 for changes in spasticity, strength, deep tendon reflexes, sensation, urinary function, and clinical disability. We found a statistically significant improvement in composite Medical Council Research (MRC) strength scores 28 days following the first infusion ($p = 0.021$). Although the second infusion did not produce a statistically significant improvement in strength, there was no significant reduction from peak strength. We found no other significant changes from baseline. These data suggest that IVIg may improve and maintain strength in patients with HIV-associated myelopathy. Based on this pilot data, we suggest a controlled study of the efficacy of IVIg in treating HIV-associated vacuolar myelopathy.

Internal Hernias: Clinical Presentation, Classification, and Management. Avi Schlager, Saber Ghiassi, and Celia Divino. Department of General Surgery, Mount Sinai School of Medicine, New York, NY.

Introduction: Internal hernia (IH) is the protrusion of a viscus through a peritoneal or mesenteric aperture. They account for up to 1% of all cases of small bowel obstruction and may be increasing in frequency. Symptoms of IH are often vague and nonspecific making clinical diagnosis difficult. Delay in diagnosis may result in a catastrophic outcome. This study describes the characteristic clinical presentation, the subtypes, and the surgical management of 49 cases of surgically proven IH at The Mount Sinai Medical Center.

Methods: A retrospective chart review of patients at our institution with the diagnosis of IH between 1994 and 2004 was conducted. Patients with previous Roux-en-Y procedures were excluded. The review yielded 49 cases of surgically confirmed IH. Data obtained included clinical signs and symptoms, radiographic findings, surgical management, and subtypes of IH.

Results: The most common subtype of IH was transmesenteric (60.0%), followed by paraduodenal and transomental (10% each). A history of prior abdominal surgery was present in 83.7% of cases. The majority of cases presented with obstructive symptoms of abdominal pain (79.6%), nausea (77.6%) and vomiting (71.4%). The most common physical exam findings were abdominal tenderness (81.6%) and distention (46.9%). The most common radiographic findings were dilated loops of small bowel (54.2% of obstructive series, 56.0% of CT scan, and 62.5% of Small bowel series), and transition zones (40% of CT scans).

Conclusion: Previously, paraduodenal hernias were reported as the most common type of IH. This study demonstrates that transmesenteric hernias are the most prevalent types of IH, especially in patients with previous abdominal surgeries. These patients often present with clinical and radiographic findings of small bowel obstruction. CT is not sensitive for detecting transmesenteric hernias. Clinicians should be mindful of IH in patients with previous abdominal surgeries and those with chronic abdominal pain without clear etiology.

The Impact of Donor Surgery Organ Extraction Time on Transplant Liver Allograft Outcomes. Avi Schlager, Anthony Patrello, Gautam Siram, and Greg McKenna. Transplant Surgery, Mount Sinai School of Medicine, New York, NY, Baylor University Medical Center.

Introduction: During a transplant donor harvest, there is a period after flushing the liver with cold preservation fluid where the organ is dissected free from the surrounding tissues and removed from the body. Often during this extraction time, the organ may be sub-optimally cooled and preserved. Cold ischemia time, the time the organ spends on ice prior to implantation, and warm ischemia time, the time from the start of organ implantation to reperfusion have been shown to affect allograft outcome. No reports have described the impact of Organ Extraction Time on donor allograft outcome.

Methods: We retrospectively obtained the data regarding donor cross-clamp times and organ removal times for over 900 cadaveric donor allograft livers for transplants performed at The Mount Sinai Hospital as well as the labs (Peak and Day-7 AST/ALT/T-Bil/PT). Data was also obtained retrospectively from a prospectively obtained database regarding donor parameters, patient and graft survival. Multivariate Cox-regression analysis was performed on the data. Results: Donor organ extraction times >30 min was associated with significantly improved 1-yr, 5-yr and 10-yr patient survival ($p=0.001$) and graft survival ($p=0.01$). Organ extraction time >30 min was associated with improvements in peak AST (585.5 vs. 666.5 $p=0.04$) and peak T-bili (5.40 vs. 6.3 $p=0.007$). Univariate analysis showed organ extraction time <30 min to be a predictor of worse allograft patient survival (Hazard ratio 1.45 with 95% CI Limits) and graft survival (Hazard ratio 1.30 with 95% CI Limits 1.057-1.607) Multivariate analysis showed organ extraction time <30 min to be an independent predictor of worse allograft function (Hazard ratio 1.36 with 95% CI Limits 1.036-1.79).

Conclusion: The data shows that not only does prolonged donor organ extraction time (>30 min) not worsen survival, but rather results in improved patient and graft survival. The explanation for this finding is currently being investigated.

A Video Project to Improve Medical Communication between Ethiopian Immigrant Patients and Health Care Providers in Israel. Joshua Schulman-Marcus, Nurit Guttman, and Anat Jaffe. Departments of Communications and Endocrinology. Mount Sinai School of Medicine, New York, NY, Tel Aviv University, Hillel Yaffe Medical Center, Hadera, Israel.

The immigration to Israel of nearly 100,000 Ethiopian Jews since 1985, most of whom came from rural villages, has presented serious communication challenges within the Israeli medical system. Many of the Ethiopian immigrants had no knowledge of Western perspectives on health or of health problems such as chronic diseases, preventive medicine, medical specialization, and nutrition. High rates of illiteracy, limited language proficiency, and different expectations of the doctor-patient relationship have led to widespread communication deficiencies that reduce the quality of care and medical outcomes. In order to aid health professionals in overcoming communication challenges with Ethiopian patients, a series of short videos will be made that both highlight common causes of miscommunication and suggest improvements. To assure that the content of the videos be as realistic as possible, interviews with doctors, nurses, patients, and health care liaisons were conducted at nine clinics across Israel that treat many Ethiopian patients. The analysis of the interview data provided incidents that will serve as the basis for the video scenarios. Several common sources of frustration and/or miscommunication were identified: 1) language barriers contributing to neglect of patient needs, 2) patients having difficulty describing their symptoms, 3) patients not understanding the purpose or instructions for prescriptions and medical tests, 4) patients frustrated because their physician didn't touch them or look at them directly, 5) not following treatment recommendations for chronic diseases such as Type II diabetes which did not exist in Ethiopia, 6) patient lack of understanding of the relevance to disease of preventive medicine and diet. From these findings several prototype scenarios will be filmed and shown to both Israeli health professionals and members of the Ethiopian immigrant community. This project is also relevant to all health professionals coping with cultural barriers to effective communication and care as a result of immigration.

Arab American Health Needs Assessment and Outreach. Sara U. Schwanke, Mary E. Foley, Elizabeth J. Garland, and Philip J. Landrigan. Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY.

Background: In the last five years, Arab American (AA) communities have come under greater scrutiny than ever before. A thorough literature review, however, yields limited research regarding the health needs of Arab residents in the US, including those of the AA community in New York City (NYC). As the number of Arab Americans in the New York metro area continues to grow, and increasing public attention is directed toward Arab communities throughout the US, more information must be obtained.

Hypothesis: AA in NYC face unidentified barriers to health care services that may be influenced by a combination of social, economic, and cultural factors.

Methods: The focus group interview is the primary research method employed. The focus group interview guide, developed from individual interviews with community leaders and social outreach providers, explores personal health perceptions and needs among community members. Two focus groups, segregated by gender, will be held at central locations in each of two Arab neighborhoods in NYC. Eligible participants must be at least eighteen years old, have immigrated to the US from an Arab country within the last 20 years, and have lived in one of the study neighborhoods at least two years.

Results: Focus group discussions will be analyzed for a variety of factors, including socioeconomic status, immigration history, proximity to care, language capabilities, and cultural beliefs that may affect accessibility and utilization of health care by members of the AA community in NYC. Given the qualitative nature of the research method, the results will be presented primarily in summary form.

Conclusions: Preliminary discussions with community leaders suggest that mental health services for the AA community are severely inadequate. A lack of Arabic-speaking providers is another frequently cited problem. The NYC AA community would benefit from health care services specifically designed to address such unmet needs.

The Effect of TFF1 Mutations on Malignant Behavior of Human Gastric Cancer Cells. Andrew D. Schweitzer, Jie-yu Zhang, Xianyang Yio, and Steven Itzkowitz. Departments of Medicine/Gastroenterology and Oncological Sciences, Mount Sinai School of Medicine, New York, NY.

Trefoil factor family-1 (TFF1) is a tumor suppressor gene in the stomach. TFF1 knockout mice all develop adenomas, with 30% progressing to invasive carcinoma. One study described eight mutations of TFF1 among 61 human gastric cancers. Two such mutations, E13K and A10D, were shown by us to lose their growth suppressor function while enhancing cancer cell invasion. This is the first example of a functional role for a mutation in any trefoil factor. The T8I and T8K mutants reported in human gastric cancer have not yet been characterized. The aim of this study is to determine how mutations at the eighth residue of TFF1, T8K and T8I, affect the behavior of human gastric cancer cells. The changes from hydrophilic threonine to either hydrophobic isoleucine (T8I) or to positively-charged lysine (T8K) are hypothesized to change the biological function of TFF1. T8I and T8K TFF1 mutants were generated by site-directed mutagenesis of E. coli cells (SURE II) that had been transfected with wild type TFF1, sequenced to verify correct point mutation, and purified from the cells. Once sufficient amounts of recombinant protein are produced, T8K and T8K will be tested in various in vitro assays including cell proliferation, apoptosis, motility and invasion through a reconstituted basement membrane (matrigel). These experiments will determine whether point mutations of the eighth residue of TFF1 that have been described in gastric cancer have functional consequences. If so, experiments will be conducted to analyze the effects of these mutations in vivo and to analyze how these mutations affect the structure of TFF1 using computational methods.

Risk Factors for Hospitalization in the First Year of Enrollment in a Home-Based Primary Care Program. Alexandra Shaw, Jeremy Boal, Joan Penrod, Tsivia Hochman, Katherine Ornstein, and Linda DeCherrie. Department of Medicine, GRECC, Brookdale Department of Geriatrics and Adult Development. Mount Sinai School of Medicine, New York, NY, Bronx VA Medical Center.

Background: Home-based primary care is growing as a model of care for homebound patients. One of the goals of such programs is prevention of unnecessary hospitalization.

Objective: To identify risk factors for hospitalization within the first year of enrollment in a home-based primary care program.

Methods: We used a retrospective chart review of $n=660$ patients in an urban visiting doctors program enrolled between 1/03 and 6/04 to collect demographic characteristics and health and functional status of patients at enrollment. We used a multi-variable logistic regression to examine these baseline factors as predictors of hospitalization within 12 months of enrollment.

Results: Males (1.9, 95% CI, 1.3-2.8), those recently hospitalized (1.6, 95% CI, 1.0-2.4) and Latinos (1.7, 95% CI, 1.1-2.7) were at increased risk of hospitalization. Patients with palliative goals of care (0.5, 95% CI, 0.3-0.9) were less likely to be hospitalized in the first 12 months after enrollment. In a subgroup analysis of patients who had no recent hospitalizations, males (1.8, 95% CI, 1.1-2.9), Latinos (1.7, 95% CI, 1.0-2.7) and those with 7 – 8 ADL limitations (1.8, 95% CI, 1.0-3.0) were at increased risk of hospitalization. Those with palliative care goals (0.4, 95% CI, 0.2-0.8) and urinary incontinence (0.7, 95% CI, 0.4-1.0) were less likely to be hospitalized.

Conclusions: Patients who are sicker at enrollment, i.e. those with more comorbidities and recent hospital stays, are at higher risk of hospitalization and may benefit from interventions to prevent hospitalization. Patients with palliative care goals are less likely to be hospitalized, which is consistent with common palliative goals. Gender and ethnicity influence hospitalization risk. More research is needed to examine potential causes for the link.

Cognitive Enhancement Through Central Thalamic Deep Brain Stimulation. Prasad R. Shirvalkar, Malika I. Seth, Nicholas D. Schiff, and Daniel G. Herrera. Departments of Psychiatry, Neurology and Neuroscience, Mount Sinai School of Medicine, New York, NY, Weill Cornell Medical College.

The biological substrates of consciousness must support states of perceptual awareness, working memory and directed attention. Previous reports have established that the central thalamus (intralaminar nuclei (ILN) and paralaminar regions) links brainstem arousal systems to cerebral cortical and basal ganglia networks crucial to the organization of wakeful behaviors; this region has also been implicated in supporting normal and pathological thalamocortical rhythms. Therapeutic treatment of neuropsychiatric disorders increasingly relies on Deep Brain Stimulation of various nuclei, although knowledge of underlying mechanisms is limited. Using precise behavioral assays and postmortem histological processing of animal brain tissue, it is possible to investigate the impact of electrical stimulation in this system. Here we focus on the central thalamus which has been proposed as a Deep Brain Stimulation target for the treatment of impaired cognitive function following non-progressive brain injuries. We studied behavioral and gene expression effects of electrical stimulation of the centrolateral nucleus (CL) of the intralaminar nuclei of the rat thalamus. Unilateral high-frequency (100 Hz) electrical stimulation of CL in awake animals produced significant improvements in performance and learning of a visual object recognition task compared to control animals. To evaluate the functional activation patterns associated with CL stimulation, we examined patterns of immediate-early gene (IEG) expression in cortical and subcortical structures. In a separate series of experiments, similar electrical stimulation of CL produced ipsilateral upregulation of c-fos and zif268 expression with laminar specificity in the motor cortex (mCtx), anterior cingulate cortex (ACC) and caudate-putamen (CP), and bilateral elevation in hippocampi at two hours following stimulation. In vivo stimulation of CL activates a wide cerebral network and may influence basic cognitive processes associated with attention and memory.

Role of VPR in HIVAN Pathogenesis. Alexandra Snyder, Mohammad Husain, Michael J. Ross, Paul Klotman, and Mary Klotman. Department of Medicine, Infectious Diseases, and Nephrology, Mount Sinai School of Medicine, New York, NY.

HIV-associated nephropathy (HIVAN), primarily affecting HIV-infected people of African descent, leads to glomerulosclerosis and microcystic tubulointerstitial disease. Although the mechanism of HIV-1 entry remains unclear, HIV-1 RNA has been found in renal epithelial cells. In HIVAN, glomerular epithelial cells, or podocytes, show a dysregulated phenotype, including dedifferentiation, hyperproliferation and apoptosis, as do renal tubular cells. Previously we have shown that HIV-1 accessory protein Nef is the major determinant of HIVAN pathology, while others report that Vpr causes mild glomerulosclerosis. We want to investigate a specific role for Vpr in renal epithelial cells. Vpr was cloned into a lentiviral vector (pHR-CMV-IRES-GFPdeltaB), which was then used to produce pseudotyped virus by transfection of 293T cells, providing gag/pol and a vesticular stomatitis virus glycoprotein (VSV.G) envelope in trans. The pseudotyped virus was used to infect immortalized human proximal tubular epithelial cells (HPT-1, established in our lab) under differentiated and undifferentiated conditions. Preliminary data demonstrates an increased apoptotic index among Vpr-infected undifferentiated HPT1 cells relative to controls. Vpr has been shown to induce G2 arrest and/or apoptosis depending on cell type, however, its mechanism has not been elucidated in kidney epithelial cells. Recently, in our lab ubiquitin-like protein Fat10 has been shown to be upregulated in HIV-infected HPT-1 cells. In ongoing studies we will investigate the role of Fat10 and Fas/FasL, which is upregulated in diseased epithelium, in the mechanism of Vpr-induced apoptosis. We hypothesize that together Nef and Vpr may induce the proliferation and apoptosis that ultimately lead to the glomerulosclerosis and tubulointerstitial disease characteristic of HIVAN.

The Regulation of Sprouty1 in Prostate Cancer. Gabriela Soriano, Analisa DiFeo, John Martignetti, Goutham Narla, Scott Friedman, Jonathan Licht, and Debra Morrison. Departments of Medicine, Hematology, Oncology, Human Genetics, and Liver Disease, Mount Sinai School of Medicine, New York, NY.

Abnormal response to growth factor signaling is a major contributor to the development and progression of many cancers. Sprouty1, a general inhibitor of the receptor tyrosine kinase/Ras/Map kinase signal transduction cascade, has been shown to be down-regulated in a variety of cancers, including prostate cancer. The attenuation of Sprouty1 expression in prostate cancer may be due to transcriptional regulation or epigenetic silencing. Previously, Sprouty1 was demonstrated to be directly regulated by the Wilms' tumor suppressor gene WT1 in the kidney. KLF6, a tumor suppressor gene in the same family as WT1, also regulates the Sprouty1 promoter in transient transcription assays. Interestingly, KLF6 is lost or mutated in a large percentage of prostate cancer cases. Due the correlation between KLF6 and Sprouty1 expression and the presence of a KLF6 binding site in the Sprouty1 promoter, we hypothesized that KLF6 regulates Sprouty1 in the prostate by directly binding to its promoter. To demonstrate a connection between these two proteins, KLF6 was transiently over-expressed in the prostate cancer cell lines PC3 and LNCaP. A variable effect on the level of Sprouty1 expression was observed by qRT-PCR. Subsequently, the opposite experiment was performed. PC3 cells were treated with small interfering RNA (siRNA) oligos to knockdown KLF6 expression. Preliminary data suggests that Sprouty1 levels decrease by approximately 30% following an 80% reduction in KLF6 expression Given this conflicting data it is not yet possible to draw a conclusion. Next, we considered that silencing of Sprouty1 is through hypermethylation of CpG islands located in the Sprouty1 promoter. Therefore, PC3 cells were treated with the demethylating agent 5-aza-2-deoxycytidine, which activates genes that may have been abnormally hypermethylated in the process of tumorigenesis. A 2 – 3 fold induction of Sprouty1 was observed by qRT-PCR. Future studies will investigate this epigenetic mechanism.

Extended Criteria Donor Livers and Graft Outcome. Anne M. Stey, Jon Chan, Ilhan Karabicak, and Sukru Emre. Recanti Miller Transplant Institute, Liver Transplant, Mount Sinai Hospital, New York, NY.

The use of extended criteria organs offers hope to transplant candidates. We analyzed a number of criteria that may determine the success of these organs as grafts including donor age, BMI, LFTs, serum sodium and bilirubin levels. Linear regression was used to determine the correlation of each of the above with postoperative length of stay, postoperative graft function as determined by postoperative LFTs and prothrombin time and length of host survival in days. We found that donor age is negatively correlated with host survival in days (m=-7.9+/- 1.74, p=0.0001). It was not related to postoperative length of stay or any parameters of postoperative graft function. Similarly, donor BMI showed a negative correlation with host survival which approached significance (m=-.27+/-.17, p=0.11). However, it was also negatively correlated with postoperative length of stay (m=-5.5+/-.88, p=0.0001). This may display the dichotomous effect of energy storage in the liver. Interestingly, measures of donor liver function, namely donor serum LFTs and billirubin, were not correlated to postoperative graft function, host survival or postoperative length of stay. There was, however, a clear negative correlation between donor serum sodium and all measures of postoperative graft function (SGPT:m=18.9+/-7.6, p=0.01 SGOT:m=24.5+/-9.2, p=0.008 prothrombin time:m=15.04+/-6.6, p=0.02). Donor hypernatremia has been cited in the literature to predispose grafts to dysfunction. However, this correlation did not extend to a correlation with survival or postoperative length of stay. In conclusion, donor age, hypernatremia and elevated BMI related to poor host survival or postoperative graft function. Unexpectedly measures of donor liver function were unrelated. This reaffirms that we must challenge what we consider factors for extended criteria organs.

The Effect of Weightlifting Exercises on Intraocular Pressure in Glaucoma Patients. Leah R. Strugatz, Lee A. Polikoff, Raul Chanis, Ashish Toor, and Janet B. Serle. Department of Ophthalmology, Mount Sinai School of Medicine, New York, NY.

Purpose: Increased intraocular pressure (IOP) is the most important risk factor in the development and progression of glaucoma. When performing certain weightlifting exercises, IOP elevation occurs due to increased choroidal volume and obstructed venous outflow. As more people perform routine weightlifting exercises, it is important to assess the effects of weightlifting exercises on IOP in glaucoma patients.

Methods: Previously diagnosed glaucoma patients who performed weightlifting exercises at least twice a week were enrolled. Eleven patients (10 Caucasian and 1 African American; mean age ± SD: 63.7 + 12.6

years), all on medical therapy for glaucoma, have participated in the study. Diagnoses included POAG 5, PDS 2, NTG 2, OHT 1, and CACG 1. IOP was measured using a pneumatonometer. Five repetitions were performed of each exercise: bench press, leg press, triceps extension, seated rows and stomach crunches. IOP for both eyes were averaged for pre-exercise, and one minute post-exercise measurements. Only the OD was used for intra-exercise IOP calculations. Statistical analysis was performed using a two-tailed t-test.

Results: Post-exercise IOP was similar to pre-exercise IOP ($p = 0.149$), following bench press, seated rows, stomach crunch and leg press. IOP decreased ($p = 0.029$) post-triceps extensions compared to pre-exercise. IOP increased intra-exercise for bench press ($p = 0.016$), from a mean of 18.32 mmHg to 21.05 mmHg, as compared to pre-exercise. Seated row ($p = 0.042$) IOP also increased intra-exercise, compared to pre-exercise IOP, from a mean of 15.27 mmHg to 16.91 mmHg.

Conclusions: Five repetitions of exercises, such as bench press, leg press, triceps extension, seated rows and stomach crunches do not appear to raise IOP in glaucoma patients within one-minute following exercise. Certain exercises, such as flat bench press and seated rows, cause transient increases in IOP. The effects of multiple repetitions during many sets of weightlifting exercises are still unknown.

Predictors of Mitochondrial Toxicity among Treatment-Experienced HIV/HCV Co-infected Patients. Malini D. Sur and Douglas T. Dieterich. Department of Medicine, and Liver and Gastroenterology, The Mount Sinai Medical Center, New York, NY.

Question: Is the risk of mitochondrial toxicity (MT) among treatment-experienced HIV/HCV co-infected patients increased by use of nucleoside reverse transcriptase inhibitors (NRTIs), age, or severity of hepatic fibrosis and steatosis?

Background: Mitochondrial toxicity of nucleoside analogs is a serious clinical concern in HIV treatment today. These drugs include NRTIs used in antiretroviral therapy and ribavirin used with peginterferon to treat Hepatitis C virus (HCV) infection. Patients receiving treatment for both HIV and HCV infection have been shown to be at an elevated risk for MT. The biochemical aging process, potentially linked to increased mitochondrial oxidative stress, may further exacerbate the risk of MT in the HIV/HCV co-infected patient, along with hepatic fibrosis and steatosis.

Methods: We examined laboratory data for 102 HIV/HCV co-infected patients, previously unsuccessfully treated for HCV, enrolled in Hepatitis Resource Network Study 004 and assigned to receive peginterferon alfa-2a and ribavirin. Serum lactate values at weeks 0, 12, and 24 after start of treatment were used to identify patients with hyperlactatemia (> 2.2 mmol/L), an indicator of MT. Binomial logistic regression was used to determine if hyperlactatemia was associated with age over 50 years, concomitant use of ddI or d4T, and baseline hepatic fibrosis and steatosis.

Results: Thirteen patients (13.5%) at week 0, 12 patients (12.5%) at week 12, and 11 patients (11.5%) at week 24 showed hyperlactatemia. Regression analysis showed neither age, use of ddI or d4T, nor severity of fibrosis or steatosis to be significantly associated with hyperlactatemia.

Conclusions: We did not observe a significantly greater risk of developing hyperlactatemia among treatment-experienced HIV/HCV co-infected patients who were above 50, used ddI or d4T, or had greater fibrosis or steatosis at start of HCV therapy. MT remains a concern in co-infected patients, and further research to identify risk factors for developing MT is recommended.

It's Like Crossing a Bridge: Barriers to Physicians Discussing Deactivating Implantable Defibrillators at the End of Life. Ezra N. Teitelbaum, Nathan E. Goldstein, Davendra Mehta, Elizabeth H. Bradley, and R. Sean Morrison. Department of Medicine/Cardiology, Brookdale Department of Geriatrics. Mount Sinai School of Medicine, New York, NY, Yale University School of Epidemiology and Public Health, Boston, MA.

Background: Implantable cardioverter defibrillators (ICDs) can prevent premature death from arrhythmias. However in the setting of advanced illness, these devices might make the dying process more painful. To avoid this, some patients may wish to have their device deactivated. Research has shown that in the context of other end-of-life discussions, physicians broach the subject of ICD deactivation with less than 30% of patients.

Objective: To identify the factors that impede physicians from engaging in ICD deactivation discussions.

Methods: Electrophysiologists, cardiologists and generalists (internists and geriatricians) were interviewed using open-ended questions to determine physicians' past experience with discussing deactivating ICDs. Transcripts of these interviews were analyzed using the qualitative method of constant comparison until no new concepts emerged in successive conversations (i.e., thematic saturation).

Results: 11 physicians (6 women and 5 men) from three states were interviewed. Physicians believed that conversations about deactivating ICDs were different than other discussions regarding end-of-life care because once the device had been deactivated, it was "like crossing a bridge" from which there was no return. Barriers to discussing device deactivation included the absence of an established physician-patient relationship, difficulty applying the theoretical importance of such discussions to practical clinical scenarios and a lack of training in end-of-life care.

Discussion: A variety of factors deter physicians from initiating conversations about ICD deactivation. Findings from this project can be used to develop strategies to enhance the quality and frequency of physician initiated ICD deactivation discussions.

Cardiac Involvement and Rate of Disease Progression in Fabry Disease—Hemizygous Males And Heterozygous Females. Jeremy J. Thaden, Maryam Banikazemi, and Martin Goldman. The Zena and Michael A. Wiener Cardiovascular Institute, The Department of Human Genetics, Mount Sinai Medical Center, New York, NY.

Fabry Disease is an X-linked lysosomal storage disorder that results from a deficiency of the enzyme alpha galactosidase A. Afflicted individuals often have angiokeratomas, peripheral pain, hypohydrosis, and suffer from a progressive small-vessel disease of the kidney, heart, and brain. Disease progression is relatively well characterized in hemizygous men, but less is known about the clinical manifestations in heterozygous women. This study will involve analyzing a database of collected echocardiograms to evaluate disease and disease progression in hemizygous males and heterozygous females. Several studies have indicated that left ventricular hypertrophy and diastolic dysfunction serve as reliable markers of disease progression in affected individuals. We expect that hemizygous males and heterozygous females will have greater left ventricular mass and diastolic dysfunction compared to normal. Additionally, because of the disease's X-linked inheritance, we expect the disease to progress more rapidly in hemizygous males than in heterozygous females. Finally, because there is a progressive and lifelong accumulation of glycolipid in afflicted cells, we expect that, among the same gender, older individuals will be more severely afflicted than younger individuals. We will compare transmitral flow (E/A ratio), an indicator of diastolic function, and left ventricular mass to age and gender-matched controls in order to characterize the changes in diastolic function and left ventricular mass relative to normal. Also, by comparing heterozygous females to age-matched hemizygous males, we will be able to better characterize disease pathology in men relative to women. Additionally, by comparing rate of change of these same parameters between hemizygous men and heterozygous women, we will be able to evaluate the rate at which the disease progresses in women with respect to men. Finally, by comparing younger individuals with older individuals of the same gender, we will be able to evaluate how the disease progresses with respect to age.

The Effect of Medicaid Eligibility Policies on Medicaid Enrollment by Low-Income Seniors. Ryan C. Ungaro and Alex D. Federman. Department of Medicine/General Internal Medicine, Mount Sinai School of Medicine, New York, NY.

Background: Many elderly Medicare beneficiaries who are eligible for Medicaid are not enrolled. With states looking to reel in rising Medicaid spending, various policy changes have been made to curtail Medicaid growth. However, little is known about the effect of state policies on Medicaid enrollment for Medicare beneficiaries.

Objectives: To determine the effect on Medicaid enrollment by Medicare beneficiaries of the Omnibus Budget Reconciliation Act (OBRA) of 1986, which liberalizes income thresholds, and section 209(b) of the Social Security Act Amendments of 1972, which allows states to establish more restrictive income and asset eligibility criteria. In addition, the effect of requiring separate State Supplemental Income (SSI) and Medicaid applications on Medicaid enrollment was investigated.

Methods: Cross-sectional analysis of the 2001 Medicare Current Beneficiary Survey examining Medicare beneficiaries 65 or older with incomes less than 100% of the federal poverty level. We modeled Medicaid enrollment as a function of residence in states applying OBRA or 209b policies, controlling for demographic and health status characteristics. Medicaid enrollment was also modeled as a function of residence in states with separate SSI and Medicaid applications.

Results: Restrictiveness of state Medicaid eligibility criteria did not appear to affect Medicaid enrollment for low-income seniors. The adjusted relative risk ratio (RR) of Medicaid enrollment for seniors living in OBRA states was 1.18 (95% CI 0.89, 1.54). The RR for subjects living in 209(b) states was 1.13 (95% CI 0.73, 1.68). The RR for subjects living in states with separate applications for SSI and Medicaid was 1.08 (95% CI 0.73, 1.55).

Conclusions: Our results suggest that 209b and OBRA policies may not significantly affect Medicaid enrollment by low-income seniors. The separation of SSI and Medicaid applications also may not affect enrollment. More research is needed to identify barriers to Medicaid enrollment for this population.

Clinical, Hormonal, and Genetic Variations in Male Pseudohermaphroditism. Peter J. Vasquez, Susan W. Baker, Robert C. Wilson, and Maria I. New. Department of Pediatric/Endocrinology, Mount Sinai School of Medicine, New York, NY.

Objectives: This study aims to characterize the clinical and hormonal profiles of subjects with male pseudohermaphroditism, and to correlate these findings to the underlying molecular genetic defect.

Background: Male pseudohermaphroditism (MPH) is defined by the presence of a 46,XY karyotype, male gonads, and ambiguity of the external and/or internal genitalia caused by incomplete virilization *in utero*. MPH can result from decreased synthesis of testosterone or from the impairment of response to androgens. Defects in androgen action are the most common cause and include mutations in the androgen receptor gene and mutations in the steroid 5alpha-reductase 2 gene. Defects in androgen synthesis are due to autosomal recessive mutations that impair any of the enzymatic reactions involved in the conversion of cholesterol to testosterone, as well as impaired stimulus of testosterone production due to defects in the hCG/LH receptor. The clinical and hormonal profiles of male pseudohermaphrodites are heterogeneous and may be correlated to specific genetic mutations. To date, the correlation of phenotype and genotype in MPH has not been fully characterized. We are evaluating an established clinic population of male pseudohermaphrodites. Retrospective medical record review is being done to obtain relevant clinical and hormonal data. If possible, subjects are asked to undergo repeat clinical, hormonal, and genetic evaluation to obtain current information. The data will be compiled and analyzed to identify genotype/phenotype correlations. Results: At this time we are in the process of gathering and analyzing data. We hope to demonstrate a correlation between genotype and phenotype in MPH. This will aid physicians in diagnosing and treating patients with MPH, and will provide a better understanding of these complex conditions to patients, their families, and physicians.

Pharmaceutical Innovation and Population Health. Steven Y. Wang and Salomeh Keyhani. Department of Health Policy, Mount Sinai School of Medicine, New York, NY.

The high price of drugs has been justified to ensure continuing pharmaceutical innovation. However the focus of current drug development has never been examined and it is unclear if current drug development serves society's health needs. This is a retrospective study examining pharmaceutical innovation in the past 14 years. A drug is innovative if it is a new molecular entity (never been marketed before in the US) and if it is given priority review by the FDA. A priority drug is considered a significant therapeutic advance, while standard review denotes a "me-too" drug. We examined trends in innovation over time and classified drugs by pharmacologic class, indication and general disease area. We also explored the association between the number of drugs developed for a disease area and the disease burden in the population. For a measure of disease burden, we used the World Health Organization's estimates of disability adjusted life years (DALY) in North America as a measure of population health. There were 366 NME's approved for 98 different indications between 1991 and 2004. One third of the drugs approved were in the infectious disease and cardiovascular categories. The most common indications for which new drugs were approved in these diseases categories were bacterial infections followed by hypertension. Over 95% of drugs approved for these two indications were "me-too" drugs. In fact, the majority of all drugs developed in the past 14 years (60%) were "me-too" drugs. Moreover, we found no association between the burden of disease as measured by DALY's and the number of drugs approved for a disease area.

Polyoma Virus Infection is a Risk Factor for Subsequent Development of Bladder Carcinoma in Immunocompetent Individuals. David B. Weinreb, Garrett T. Desman, David E. Burstein, James Godbold, and Edward Johnson. Departments of Pathology, and Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY.

Despite various reports of polyoma virus (PV) DNA sequences in tumors, there has been no study statistically linking PV infection to tumor etiology. Here, we have performed a cross-sectional study of 3782 immunocompetent patients having had urine cytologic analyses. One hundred and thirty-three of these patients were reported to have PV-infected urothelial cells in the urine, a finding previously considered to be clinically insignificant in immunocompetent patients. We determined that PV infection of urothelial cells is associated with a diagnosis of bladder carcinoma (Odds ratio = 4.813, $p<0.001$). Additionally, we considered only patients for whom the PV-infected cells were identified prior to the earliest diagnosis of bladder carcinoma; the association remains statistically significant (Odds Ratio = 3.419, $p<0.001$). We conclude that identification of PV-infected cells is highly predictive of a subsequent diagnosis of bladder carcinoma. The polyoma T-antigen binds to the p53 gene product, inhibiting its function but also stabilizing it such that an increase in p53 can be detected by immunohistochemistry. Here, we examine six cases of renal transplant patients with allograft dysfunction resulting from PV infection of the non-native kidney. In all cases, immunohistochemistry demonstrated p53 expression specific to the renal tubular cells with cytopathologic features indicative of PV infection. This result suggests that binding of p53 by T-antigen occurs in PV infected cells. Collectively, these data suggest that PV infection is a risk factor for bladder carcinoma and that sequestration of p53 by T-antigen may be part of the mechanism by which PV infection promotes oncogenesis.

A Community Outbreak of Legionnaires' Disease. Kristin M. Wilson, George James, Rosalyn O'Loughlin, Lon Kightlinger, Hill Nicholas, Matt Werpy, Josh Clayton, and Mathew R. Moore. Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY, Respiratory Diseases Branch Division of Bacterial and Mycotic Diseases, Centers for Disease Control and Prevention, South Dakota Department of Health.

Background: Seven cases of community acquired Legionnaires' disease were reported in Rapid City, South Dakota. Dates of onset for these cases ranged from May 23 to July 7, 2005. Five patients were hospitalized, 1 died. An epidemiologic and environmental investigation was conducted to attempt to identify the source of the outbreak.

Methods: Aerosol producing devices that could act as potential sources of Legionella in the town were identified. Water samples and biofilm swabs of these potential sources, as well as samples from the case patients' homes were obtained and sent to the CDC Respiratory Diseases Legionella Laboratory for analysis. A case control study was conducted with the 7 cases matched to 4 controls each by race and underlying medical condition. Cases and controls were asked about exposures to potential aerosol producing devices, places they had traveled to in town and the routes they used to get there.

Results and Conclusions: All 7 cases were positive for Legionella pneumophila serogroup 1 (Lp1) by urine antigen tests. A clinical isolate available from one patient was found to be Lp1 MAb pattern (1,2,5,7). 50 environmental samples were obtained, including water samples and swabs from the 6 case homes, 6 area cooling towers, and 1 decorative fountain. All of the cooling towers and two patient homes tested positive for Legionella, but none matched the Mab pattern of the suspected outbreak strain. In the matched case control study analysis, no statistically significant differences were found between the cases and controls that could implicate a source of the outbreak. At this time, no source of the outbreak has been identified either through environmental sampling or epidemiologic analysis. Recommendations regarding remediation of the positive cooling towers and residences have been made.

Measuring Patient Satisfaction: An Emergency Department Experience. Leigh M. Wright, Jennifer V. Norton, and Ruben E. Olmedo. Departments of Nursing, Toxicology, and Emergency Medicine, Mount Sinai School of Medicine, New York, NY.

Patient satisfaction is a subjective quantity, having less to do with the quality of medical care received than the perception of how well that care was delivered. Customer satisfaction is becoming an important factor in measuring successful medical care. It is commonly accepted that patient satisfaction levels are indicators of future patient behaviors and health care choices. In emergency departments, patient satisfaction takes on added significance since often a patient's primary contact with an institution occurs within the emergency department. In 2003, the Department of Emergency Medicine (ED) at Mount Sinai Hospital initiated a Customer Service Design Team to implement strategies for improving patient satisfaction. Some of the strategies focused on key areas of personnel courtesy, patient overcrowding, patient waiting times, and communication during the ED visit. The present study evaluated which factors may have contributed to overall patient satisfaction and determined areas in need of improvement. A customer satisfaction instrument was created in English and Spanish. The survey was distributed to a convenience sample of 220 patients at the time of discharge. Answers were given using a 5-point Likert scale, free response and self-reported arrival/discharge times and demographic information. When asked to rate their overall satisfaction level, more than 80% of the patients responded with "satisfied" or "very satisfied." Doctor, nurse and registrar courtesy also achieved high satisfaction ratings. However, only 50% of patients stated that the speed of their visit was "faster" or "much faster" than the amount of time they expected to spend in the ED. This may indicate that improving on patients' ED length of stay is a potential source for improving patient satisfaction.

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Erratum

In the May issue, Mt Sinai J Med 2006; 73(3):622–626, the affiliation of the first author, Dr. Yih-Hsin Chang, should read: School of Medical Laboratory and Biotechnology, Chung Shan Medical University.

Dean's Lecture

Planar Cell Polarity Signaling:

A Common Mechanism for Cellular Polarization

ANDREAS JENNY, PH.D. AND MAREK MLODZIK, PH.D.

Abstract

Epithelial cells frequently display—in addition to the common apical-basolateral polarity—a polarization within the plane of the epithelium. This is commonly referred to as planar cell polarity (PCP) or tissue polarity. Examples of vertebrate PCP include epithelial patterning in the skin and inner ear, and also the morphogenetic movements of mesenchymal cells during convergent extension at gastrulation. In *Drosophila*, all adult epithelial structures of the cuticle are polarized within the plane. This review presents recent results and new insights into the molecular mechanisms underlying the establishment of PCP, and compares and contrasts the intriguing similarities between PCP signaling in *Drosophila* and vertebrates.

Key Words: Frizzled, planar cell polarity, tissue polarity, convergent extension, organ of Corti, Drosophila, mouse, zebrafish.

Introduction

EPITHELIAL CELLS are polarized in multiple ways. Apical-basolateral polarity (perpendicular to the plane of the epithelial sheath) enables a cell to directionally transport molecules across a cell layer (e.g., in the gut, kidney and glands) and selectively secrete extracellular matrix components to form a basal lamina (1). To perform many of their functions, epithelia frequently also have to be polarized within the plane of the epithelium. The latter polarization is commonly referred to as epithelial planar cell polarity (PCP) or tissue polarity; it allows cells to form structures that require not only positional, but also vectorial information.

The cellular consequences of PCP signaling range from coordinated organization of cytoskeletal elements in single cells to complex migration of groups of cells. Examples of PCP in vertebrates can be very obvious, as in the ordered arrangement of scales on fish or feathers of birds, and hairs of mammalian skin. Less visible examples are the cilia of the respiratory tract and oviduct, or the stereocilia of the sensory epithelium of the organ of Corti in the vertebrate inner ear. Aberrant PCP of the sensory epithelium in the organ of Corti leads to deafness (2). Furthermore, the complicated movement of mesenchymal cells during gastrulation (called convergent extension), which leads to the elongation and thinning of the body axis, also depends on correct PCP signaling (3–10).

PCP signaling is, however, best studied in *Drosophila melanogaster*, mainly because of the versatility of the fly as a model system. In *Drosophila*, PCP can easily be seen on several external adult structures such as the bristles on the thorax or the precisely aligned hairs on wing cells (Fig. 1A; 11). In addition, the facet eye of insects also shows characteristics of PCP, with its precise arrangement of the building blocks, the ommatidia, with respect to each other and the general axes in each eye (9). Genetic and molecular studies of *Drosophila* led to the identification of a signaling network directing PCP establishment. In recent

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years it has become apparent that the PCP signaling module is highly conserved and is essential for PCP establishment in many vertebrate contexts, including the inner ear and convergent extension during gastrulation and neurulation (6, 12).

Discovery of the mechanism of PCP signaling and its conservation from insects to ascidians and mammals is one of the most exciting topics of developmental biology today (13). In this review we discuss PCP signaling in *Drosophila* and compare it with recent findings in the vertebrate field. In particular, we address intriguing parallels in PCP establishment between fruit flies and vertebrates on the mechanistic level and discuss novel findings that suggest a link between PCP signaling and ciliary diseases.

Planar Cell Polarity in *Drosophila*

Many adult structures of *Drosophila* show an easily visible planar polarization. For example, each cell of the wing blade grows a distally pointing, actin-rich hair close to its distal vertex (Fig. 1A; 11, 14). This process of hair orientation relies solely on directionally driven cytoskeletal rearrangements, without an apparent requirement for a transcriptional response (in contrast to other tissues, see below [15, 16]). In the absence of proper PCP signaling, the wing hairs form in the middle of the cell and are misoriented, or multiple hairs form on a single cell. On the thorax and abdomen, sensory bristles are aligned along the anterior-posterior (A-P) axis and point towards the rear end of the fly body (for details of PCP on the abdomen, see refs. 17–20). The sensory bristles of the thorax develop during pupal stages and consist of 4 different cells that originate from a single sensory organ precursor (SOP) cell in two rounds of asymmetric division. In order for the bristles to be oriented with the body axis, the SOP cell has to divide along the A-P axis. PCP signaling is required to align the spindle and the asymmetrically distributed cell fate determinants Numb and Neuralized with the A-P axis (21–24). In the absence of PCP signaling, the SOP cell still divides asymmetrically; however, the axis of division is randomly chosen and thus the bristle is ultimately randomly oriented.

A less obvious, but nevertheless more complex polarization is found in the facet eye of *Drosophila* (and in insects in general). Within each facet or ommatidium—the modular building block of the eye—the rhabdomeres (light-sensitive organelles) of the six outer (R1–6) and two inner (R7/8) photoreceptors are organized in a trapezoid pattern that is invariable from ommatidium to ommatidium (Fig. 1C; 25, 26). Furthermore, each ommatidium is aligned with the A-P and dorso-ventral (D-V) axes. Such an elaborate geometric organization is required for proper image formation after wiring of the photoreceptor axons in the underlying lamina, medulla and brain lobes. Due to the curvature of the eye surface, photoreceptors of a single facet "see" different points in space, and therefore corresponding photoreceptor neurons of neighboring ommatidia, which "see" the same point in space, project together to represent a single point in space on a topographic map in the brain (27). The precise orientation of each ommatidium and its photoreceptors along the A-P and D-V axes is thus essential for the accurate processing of visual information in the brain. In the absence of PCP signaling, this precise alignment is lost, even though the individual building blocks still form (Fig. 1D).

How is such complex organization established? The adult eye of *Drosophila* develops from the eye imaginal disc, a single-layered epithelium that derives from the embryonic ectoderm. During the third larval instar, a wave of differentiation, the morphogenetic furrow (MF), sweeps from posterior to anterior across the eye disc, leaving in its wake differentiating photoreceptor clusters that mature progressively (28, 29). At the time of PCP signaling, each precluster consists of the R8 founder cell and photoreceptor precursor cells R2/R5 and R3/R4 (Fig. 2A). The preclusters are symmetric with respect to the R3/R4 precursors, with the R3 precursor (orange in Fig. 2A) closer to the midline of the eye (equator) and the R4 precursor adjacent on the polar side (blue). Asymmetry is first seen when the preclusters start to rotate in opposing directions dorsal (clockwise) and ventral (counterclockwise) of the equator from row 4 onward (Fig. 2A). About 9 or 10 rows posterior to the MF, the clusters have rotated by 45°. By that time, the remaining photoreceptor precursors R1/R6 and R7 are recruited as well, and the clusters continue to rotate to complete a 90° rotation with respect to their original position. Ultimately, the opposite direction of rotation leads to mirror-symmetric dorsal and ventral halves of the adult eye with asymmetric positioning of the R3 (anterior, polar position) and R4 cells (posterior, more equatorial) within the trapezoid formed by the 6 outer photoreceptors (Fig. 1C and 2A; 25, 26, 30–34).

The different chiral forms, distinctive in the adult eye, can already be anticipated during the third larval instar. Just prior to the beginning of precluster rotation (about row 4/5 behind the morphogenetic furrow), asymmetries in molecular markers can be detected. A *lacZ* enhancer trap under control of the Delta (Dl) promoter is expressed more strongly in R3 than in R4 (35–37), while *m∂0.5>lacZ*—a short enhancer fragment of the Notch (N) target gene m∂—is expressed at higher levels in R4 (see below and ref. 38). These differences between the R3 and R4 cells are the result of PCP signaling and direct the subsequent rotation and asymmetric positioning of R3 and R4 in the adult eye.

Molecular Control of PCP Signaling

Most components of the PCP signaling cassette have been discovered in genetic screens in *Drosophila*. A subgroup of PCP genes—the core PCP genes—are required for PCP signaling in all tissues, while others are required only in certain tissues and therefore probably reflect more downstream effectors (see below). A characteristic common to mutations in core PCP genes is that the structures in question still form correctly, but that their orientation or alignment is perturbed (Fig 1).

In the eye, the cell fate specification of the R3 and R4 photoreceptors is key to the precise ommatidial and tissue polarity in the adult. After recruitment of the R2/R5 and R3/R4 precursors into the precluster—a process requiring the Notch and EGFR signaling pathways—the R3 and R4 precursors are subspecified as such by the action of the transcription factors Seven-up (36) and Spalt (39). PCP signaling is then required to signal the binary switch of R3 versus R4 fate and thereby determines the direction of rotation and positioning of the photoreceptors within the mature cluster. Genetic mosaic analysis of PCP components has revealed that the PCP genes are required for signaling only in the R3 or R4 precursors, but not other photoreceptors (see Table 1 and below; 40–45).

It has been proposed (46, 47) that a PCP signal that has previously been specified emanates from the dorso-ventral midline by a complex signaling interplay between the (canonical) Wingless, JAK-Stat and Notch pathways (ultimately leading to N activation at the equator of the eye [48]). Due to its position closer to the equator at the time of signaling, the R3 precursor receives a slightly higher signal than the more polar R4 precursor. Even though the nature of the ligand is still unknown, it has been shown that the seven-pass transmembrane protein Frizzled (Fz; Figs. 2B and C, and the Table) acts as PCP signal receptor (40, 49, 50). The signal is then transduced to Dishevelled (Dsh, Dvl in vertebrates), which has the structure of a typical adapter protein with three protein-protein interaction domains (DIX, PDZ and DEP domains), of which the PDZ domain has been shown to bind Fz (51–54). The signal then travels via the small GTPases Rho and Rac (15, 55), the Ste20-like kinase Misshapen (Msn; 56) and a JNK/MAPKinase cascade (52, 57) to the nucleus. The elicited transcriptional response specifies the R3 fate. One of the target genes in R3 is Dl, which then signals to its receptor N in the neighboring R4 precursor. N signaling in R4 leads to R4 fate specification (38, 42, 58). The Dl/N signaling thus reinforces an initially small difference in Fz/PCP signaling between the R3 and R4 precursors.

The balance of Fz activity in R3 and R4 appears to be tightly regulated on two levels: First, the golgi-resident, type II transmembrane protein *four-jointed* (*fj*) and the atypical cadherins *fat* (*ft*) and *dachsous* (*ds*) presumably form a system that modulates Fz activity, creating an activity gradient (59–63). Second, Fz activity is actively controlled between R3 and R4 (see below). *fj*, *fat* and *ds* clones in the eye (59–62) lead to chirality inversions at the polar (*fj*, *fat*) or equatorial (*ds*) border of the clones (and randomization within *ft* and *ds* mutant clones). Genetic and histochemical studies have led to the conclusion that Fj and Ds antagonize Fat, which then in turn acts positively on Fz signaling (61). It is likely that similar scenarios involving *fat*, *ds* and *fj* act in most if not all tissues in *Drosophila*. Evidence for potential upstream input via the Fat, Ds and Fj interactions on Fz signaling is also reported for the wing and the abdomen, although the proposed interactions are not always identical (19, 64, 65). How Fz activity is regulated through potential global cues remains one of the most elusive problems in PCP generation.

Intracellular PCP Factors and Their Interactions

Evidence for a tight regulation of Fz signaling at the level of R3 and R4, or in neighboring wing cells, originates from the analysis of fly mutants. Genetic screens identified four additional core PCP genes (Figs. 2B and C): the atypical cadherin Flamingo (Fmi; aka. Starry-night, Stan; 66, 67), the four pass transmembrane protein Strabismus (Stbm; aka. Van Gogh, Vang; 41, 68) and the cytoplasmic proteins Diego (Dgo; 69) and Prickle (Pk; 70, 71). Dgo can bind Dsh and it stimulates Fz-PCP signaling activity (43, 69). Stbm and Pk both can antagonize Fz-PCP signaling (41, 43, 68, 69, 72). Pk is recruited to the cell membrane by Stbm (44, 73, 74) and also interacts with Dsh (43, 72). Binding of Dgo and Pk to Dsh is mutually exclusive, which is a molecular explanation for the antagonistic effect of Pk and Dgo on Fz-PCP signaling (43).

Genes acting positively on R3 fate specification and promoting Fz activity, such as Fz, Dsh, and Dgo, are genetically required only in the R3 precursor (Table; 40, 43, 75). On the other hand, Stbm and Pk antagonize R3 specification and Fz activity and are genetically required in R4 (41, 44, 75). The only gene known to date that is required in both precursors is Fmi, which—as an atypical cadherin—mediates homophilic adhesion (67), consistent with its early positive requirement for Fz-PCP signaling in R3 and its later function in R4 specification (45). Besides the PCP factors, components of Notch signaling also show specific cellular requirements in the R3/R4 pair: Whereas Dl is required in R3 (as a transcriptional target of Fz/PCP signaling), Notch is only required in R4 (42, 58). Analogous interactions among the PCP factors occur in wing cells, with the exception that Dl and Notch play no role there (see below).

Differences between the Eye and Wing

As mentioned above, PCP signaling in the wing requires a reorganization of cytoskeletal elements and does not require a transcriptional response (15). However, in addition to the core PCP genes, tissue-specific effectors are essential for correct initiation of the actin hairs. Mutations in genes such as *fuzzy*, *inturned*, *tricornered*, *multiple-wing hairs* or *fritz* (which are often referred to as secondary PCP genes) lead to the formation of multiple wing hairs per cell (11, 76). Furthermore, Rho kinase (Drok), an effector of RhoA, also plays a critical role linking Fz-PCP signaling to actomyosin contractility via the regulation of Myosin Regulatory Light Chain (MRLC or Sqh) and Myosin II (MyoII; 77).

In the eye, the specification of the R3 and R4 cell fates also regulates the direction of ommatidial rotation and associated cytoskeletal changes. As with the wing, some aspects of this appear to be governed by common effectors like Drok (77). Ommatidial rotation is further controlled by an eye-specific secondary PCP gene, *nemo* (78), and additional regulatory input via epidermal growth gactor-receptor (EGF-R) signaling (79–81). How the tissue-specific secondary PCP genes regulate the respective downstream processes is poorly understood at best, and their link to the core PCP factors is also unknown. These are some of the most interesting questions to be addressed in the future.

Planar Cell Polarity Signaling in Vertebrates

The highly intriguing parallels between *Drosophila* and vertebrate PCP have recently received considerable attention. Mice lacking mFz6 show irregular hair patterning and swirls on their fur, instead of a regular parallel hair orientation (82). This is intuitively very similar to the aberrant actin hair orientation on *fz* mutant fly wings. Much better studied, however, are PCP establishment in the vertebrate inner ear and the process of convergent extension during gastrulation and neurulation (e.g., 7, 83).

Vertebrate Inner Ear

Within the organ of Corti in the mammalian cochlea, stereocilia bundles on the luminal surface of inner and outer rows of mechanosensory hair cells (Fig. 1E; 91) are stereotypically arranged in a chevron-like pattern. From one cell to the next, the chevrons are precisely aligned. The correct orientation of the hair bundles is a prerequisite for proper hearing, because the bundles are directionally sensitive to the sound waves traveling along the cochlea (for detailed reviews see 2, 7, 8). Strikingly and characteristic for aberrant PCP signaling, mutations in the mouse orthologs of several fly core PCP genes affect the orientation of the cilia chevrons without affecting their actual structure. The best-studied mutation, *looptail* (*lp*), maps to *vangl2* (84, 85), one of the two mouse orthologs of *stbm/vang* (see Fig. 1F for its aberrant organization of the stereocilia on its sensory neurons). Similar abnormal hair polarization is also found when *celsr1* (86), one of the *fmi* orthologs, is mutant or in double knock-outs of *dvl1* and *dvl2* (87). The similarity of PCP signaling in mouse and *Drosophila* is further supported by strong genetic interactions between *dvl* and *vangl2* (87). As in the fly, the signal required for cilia orientation is unknown. Even though Wnt7a is expressed in a gradient across the inner and outer hair cells (8) and Wnt7a can affect planar cell polarity in cochlear explant cultures (88), several single *wnt* have no ear PCP phenotype, a fact that has been attributed to redundancy (8, 88). However, it has recently been shown that a mouse Fz3 and Fz6 double knock-out shows typical PCP phenotypes in the inner ear (89).

At least two additional genes have been identified that can affect sensory hair polarity in the inner ear (at least in the outer hair cells): *protein tyrosine kinase 7* (90) and *scribble* (91). However, their fly orthologs, *offtrack* and *scrib*, have not yet been implicated in PCP signaling. It will be important to carefully test them for potential genetic interactions with PCP genes in *Drosophila* in order to determine whether *scribble* and *ptk7* are vertebrate-specific PCP factors.

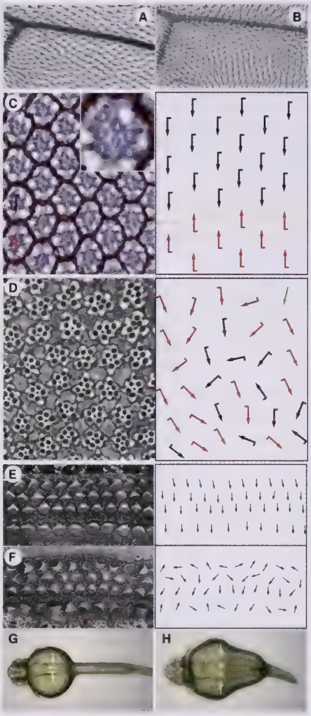

Fig. 1. Characteristics of planar cell polarity phenotypes are conserved between flies and vertebrates. All examples show mutant phenotypes of Stbm/Vang family members. Part of an adult wild-type (**A**) and a mutant wing (**B**). In contrast to wild-type, where wing hairs point towards the distal end of the wing (to the right in both pictures), in the mutant wing the hairs form whorls and waves. **(C, D)** Tangential sections through an adult *Drosophila* eye of wild-type (**C**) and mutant (**D**). In each scheme on the right, the dorsal and ventral ommatidial clusters are represented by black and red arrows, respectively. (**C**) In wild-type, the ommatidia are arranged in a mirror symmetric pattern with respect to the equator (yellow line in scheme on the right) and R3 is positioned at the anterior tip of the trapezoid, while R4 is more posterior (see inset with numbered R-cells; note that R8 is below R7 and thus cannot be seen.). In the *stbm/vang* mutant eye, the ommatidia form mostly correctly, but their mirror symmetrical arrangement is lost with both chiral forms forming at random. In addition, symmetrical clusters (green arrow) and misrotated clusters are present. **(E, F)** Scanning electron micrographs of part of the organ of Corti in the inner ear of a wild-type (**E**) and a *vangl2* (the mouse ortholog of *stbm/vang*) mutant mouse (**F**), showing the single inner and three outer rows of sensory hair cells with the characteristic chevrons formed by their stereocilia. The schematic on the right emphasizes the loss of polarity in the *vangl2* mutant. **(G, H)** Dorsal view of a wild-type (**G**) and maternal-zygotic *tri* (*stbm/vang* ortholog) (**H**) mutant zebrafish. Compared to the wild type, the shorter, but wider body axis is apparent in the mutant. The lateral borders of the notochord and the somites are marked with bars and arrows, respectively.

Figs. 1E and 1F reproduced with permission from Montcouquiol M, Rachel RA, Lanford PJ, et al. Identification of Vangl2 and Scrb1 as planar polarity genes in mammals. Nature 2003; 423:173–177 (91) and Figs. 1G and 1H reproduced with permission from Ciruna B, Jenny A, Lee D, et al. Planar cell polarity signalling couples cell division and morphogenesis during neurulation. Nature 2006; 439(7073):220–224 (74).

Convergent Extension

During vertebrate gastrulation and neurulation, convergent extension (CE), in which mesodermal and neurectodermal cells migrate towards the midline and intercalate there (6, 10, 83, 92), leads to a significant elongation of the body axis (Fig. 1G; 74). In order to migrate, the cells elongate along the axis of migration and become polarized with high protrusive activity at the medial or both ends. Several zebrafish mutants and morpholino oligonucleotide mediated knock-downs in zebrafish and *Xenopus* have demonstrated the involvement of the PCP signaling pathway in convergent extension. Mutants in the *trilobite* gene, the major ortholog of *stbm/vang* (Fig. 1H; 74, 93), as well as in *wnt11* (94), *wnt5* (95) and knockdown of Pk (96–98), Fmi (99), Diversin (a potential ortholog of Dgo), and Jun N-terminal kinase (JNK) (100) all lead to aberrant convergent extension resulting in a shorter axis, with a wider body (e.g., compare Figs. 1G and H). Due to the broadened meso- and neurectoderm, the neural tube frequently fails to close, as with common human birth defects (101, 102). It recently became clear that not all of the extension of the body axis during gastrulation is due to cell intercalation. A significant amount of the extension is due to directional orientation of mitosis along the antero-posterior axis of the dividing mesodermal cells (103). Perhaps like the SOP division in *Drosophila* (see above), the spindle alignment with body axis is controlled by the PCP pathway. In zebrafish embryos injected with Xdd1, a dominant negative form of Dishevelled, and to a lesser extent in *wnt11* and *tri* mutants, the orientation of the axis of cell division is randomized, and thus directional growth contributes less to the extension of the body axis (103).

Yet a different link between cell division and PCP signaling during neural tube formation in zebrafish has recently been described (74). The

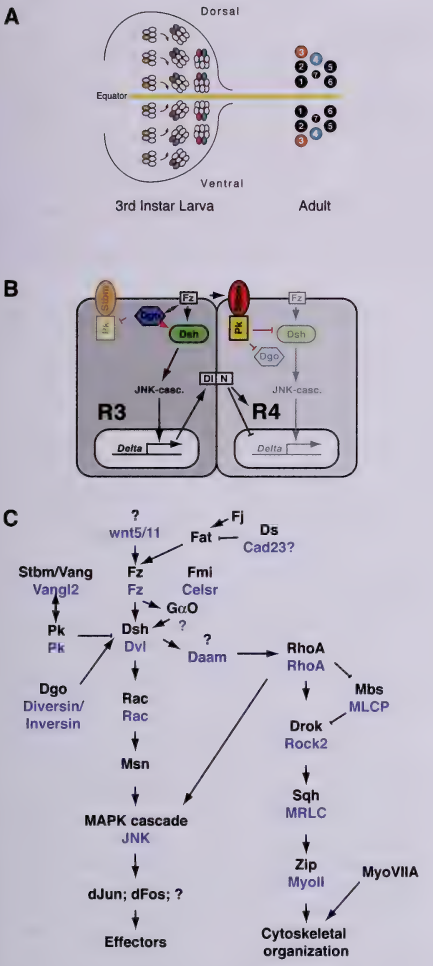

Fig. 2. (**A**) Schematic of third instar *Drosophila* eye imaginal disc with dorso-ventral (D-V) midline or equator, in yellow. Anterior is left and dorsal up. Initially, ommatidial preclusters are symmetrical. PCP signaling leads to the determination of R3 (orange) and R4 (blue), followed by a 90° rotation of clusters towards the equator. In the adult, the rhabdomeres of the photoreceptors are positioned in mirror-symmetric trapezoids with R3 anterior to and polar of R4. (**B**) Schematic of PCP signaling in R3 and R4. Signaling of Fz through Dsh and a JNK cascade leads to specification of R3. In R4, Fz signaling is antagonized by Stbm and Pk. In a second step, the signaling difference between R3 and R4 is reinforced by Dl and N (N then specifies the R4 fate). See text for details. (**C**) Schematic summarizing the genes involved in PCP signaling in *Drosophila* (in black) and in vertebrates (compiled from different tissues, blue).

neural plate folds to appose apical surfaces of opposite sides (neural keel). As the cells divide, they round up and lose polarity. After division, both cells repolarize, and while the mother cell reintegrates ipsilaterally, the daughter cell crosses the midline of the embryo and integrates into the neuroepithelium on the contralateral side. In maternal-zygotic *tri* mutant embryos, the daughter cell fails to cross the midline and cannot integrate into the neuroepithelium. Therefore, many unpolarized cells remain in the middle of the future neural tube, which results in an enlarged, unorganized neural anlage. Intriguingly, inhibition of cell division in maternal-zygotic *tri* embryos suppresses this defect, suggesting that PCP signaling is required to coordinate the cellular behavior of newly divided cells and promote their repolarization and integration (74).

Towards a Molecular Understanding of PCP Signaling

Ultimately, PCP signaling leads to polarization of a cell along an axis that is indicated by differential distribution of an activity or molecular marker along this axis. Earliest candidates for asymmetrically localized proteins are the PCP factors themselves. In the fly eye and wing, prior to PCP signaling, the PCP components are localized uniformly around the apical cellular junctions (104–107). In the wing, this apical localization depends on the transmembrane proteins Fz, Stbm and Fmi (107). In these mutant backgrounds, the other proteins, including Dsh, are not targeted to the apical circumference, a prerequisite for PCP signaling (108); in the eye, the interplay between PCP factors contributing to apical localization appears to be more complex (105). As a result of PCP signaling, the subcellular protein distribution becomes further refined. The PCP factors acting positively on Fz/PCP signaling, such as Fz itself, Dsh and Dgo, become localized distally within wing cells and are absent from the proximal side (Fig. 3A and the Table; 104, 105, 107). In contrast, the proteins acting antagonistically to Fz signaling—Pk and Stbm—become enriched at the proximal side of wing cells (106). Based on its requirement for its own proximal and distal enrichment, Fmi is so far the only protein known to become enriched at the proximal and distal ends of the cells (67). Ultimately, PCP signaling thus leads to the asymmetric distribution of its own signaling components across the border of two neighboring wing cells (Fig. 3A). Analogously in the eye, Fz/Dgo are enriched on the apical, polar side of the R3 cell and absent from the equatorial side of R4 (105, 106). In contrast, Stbm shows a complementary localiza-

TABLE

PCP Genes and Their Relationships

PCP gene	Tissues affected in *Drosophila*	Processes affected in vertebrates#	Molecular features	localization in *Drosophila* wing cells/eye	R3/R4 requirement	References
frizzled (fz)	all adult tissues	CE, inner ear, epidermis	seven-pass transmembrane receptor, binds Wnt ligands, binds Dsh, recruits Dsh and Dgo to membrane	distal/polar R3	R3	(49-51, 107, 129-131)
dishevelled (dsh)	all adult tissues	CE, inner ear	cytoplasmic protein containing DIX, PDZ, DEP domains, recruited to membrane by Fz, binds Fz, Pk, Stbm and Dgo	distal/n.d.	R3	(51-53, 94, 104, 132-134)
flamingo (fmi)/ starry night (stan)	all adult tissues	CE, inner ear	Cadherin with seven-pass transmembrane receptor features, homophyllic cell adhesions	proximal + distal n.d.	R3 +R4	(45, 66, 67, 86, 99, 135)
diego (dgo)	eye, wing, notum in GOF*	CE	cytoplasmic Ankyrin repeat protein, recruited to membrane by Fz, binds Dsh, Stbm and Dgo	distal/polar R3	R3	(43, 69, 105, 125)
strabismus (stbm)/ Van Gogh (Vang)	all adult tissues	CE, inner ear	novel 4-pass transmembrane protein, binds Pk, Dsh and Dgo, recruits Pk to membrane	proximal/eq. R4	R4	(41, 44, 68, 73, 74, 84, 85, 136-138)
prickle (pk) (a.k.a. *prickle-spiny legs*)	all adult tissues	CE	cytoplasmic protein with 3 LIM domains and PET domain, recruited to membrane by Stbm, physically interacts with Dsh, Stbm and Dgo	proximal/n.d.	R4	(44, 70-73, 96-98)
Fat (Ft)	all adult tissues	?	Proto-cadherin, heterophyllic interaction with Ds, binds Atrophin	uniform (AJ)	R3	(19, 61, 62, 64, 139, 140)
dachsous (ds)	all adult tissues	inner ear (structural)	Proto-cadherin, heterophyllic interaction with Fat	uniform (AJ)	R4	(19, 61, 62, 64, 140)
four jointed (fj)	all adult tissues	?	type-2 transmembrane or secreted peptide possibly functions in Golgi to modify Ds	?		(59-61, 64, 140)
RhoA	eye, wing*	CE	small GTPase, acts downstream of Dsh	n.d.	R3	(55, 141)
rho kinase (drok)	eye, wing	CE	Ser-Thr kinase	n.d.		(77, 142)
misshapen (msn)	eye, wing, notum*	?	STE20-like S/T protein kinase, acts downstream of Dsh	n.d.	R3	(56)
widerborst	wing*	?	B' regulatory subunit of PP2A	diffuse distal/n.d.		(117)

# only tested tissues mentioned, combination of analysis in *Xenopus*, zebrafish and mouse
* other tissues were not tested
n.d. not determined

tion pattern and is enriched on the equatorial side of R4 and absent from the polar side of R3 (Fig. 3B; 106; in the eye, the R3/R4 specific distribution of Pk and Dsh remains to be determined). The subcellular localization pattern of the PCP proteins with respect to the R3/R4 cell interface parallels the genetic requirement of their genes (e.g., factors required in R3, like Fz and Dgo, localize to the R3 side of the R3/R4 cell border).

A similar distribution of PCP proteins has been described during the asymmetric cell division of SOP cells, during notum development. Pk and Stbm localize to the anterior cortex, while Fz is enriched at the posterior side of the SOP cell (Fig. 3C; 22, 109). Interestingly, Fmi remains distributed uniformly around the SOP cell cortex (110).

PCP protein localization has recently also been shown to be asymmetric in vertebrate cells. In the inner ear sensory hair cells, GFP-Dsh localizes to the distal side of the cells, where—as in the fly wing—the actin-rich stereocilia are localized (Fig. 3D; 87). Analogously, Vangl2, the mouse Stbm ortholog, localizes to the opposing, proximal side (111). Intriguingly, Fz3 and Fz6 colocalize with Vangl2 and thus show an unexpected difference between PCP signaling in *Drosophila* and vertebrates (89, 111). Furthermore, in the zebrafish notochord and neurectoderm, GFP-Pk localization is enriched on the anterior side of the cells (74). During cell division in the neurectoderm, Pk becomes cytoplasmic and—after division—regains its asymmetry (Fig. 3E). This anterior enrichment is PCP signaling dependent. As in *stbm* mutants in *Drosophila*, in maternal/zygotic *tri* mutants or *wnt11*/*wnt*5/wnt4 triple mutants/knock-downs, Pk membrane localization is lost (74).

Generation of Asymmetric PCP Protein Localization

Using a mathematical model, it has been shown that four components of the PCP system and an initial asymmetry that might be generated by *four-jointed*, *fat* and *dachsous* are sufficient to establish and maintain the asymmetries in protein localization in the fly wing (112). The model is based on Fz recruiting Dsh to the membrane (51, 104, 107), and Pk/Stbm inhibiting Dsh recruitment

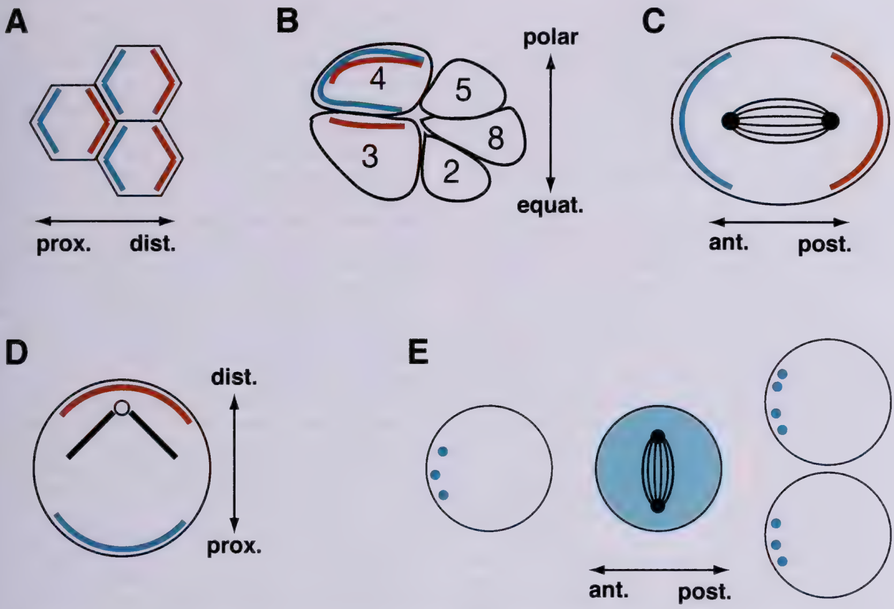

Fig. 3. Subcellular PCP protein distribution in wing cells (**A**), the eye (**B**) and SOP cells (**C**) of *Drosophila*; mouse sensory hair cells of the organ of Corti (**D**); and zebrafish neurectodermal cells (**E**). For each case, the corresponding axis is indicated by arrows. Fz/Dsh/Dgo are indicated in red, while Stbm-Vang and Pk are in blue. Note that, depending on the tissue, only a subset of the respective proteins have been analyzed. (See text for details. In addition, Fz3 and Fz6 colocalize with Vangl2 in the organ of Corti.) (**E**) In zebrafish, Pk is cytoplasmic during cell division, but regains polarity after separation of the daughter cell.

by Fz (44, 72, 73). Furthermore, the model requires an interaction of Fz with Stbm across cell membranes. Under these conditions, the model can explain many phenotypes of PCP mutant clones. However, *in vivo* there are clearly more than four PCP genes required for correct PCP establishment. Thus the model is not complete, and there must be backup mechanisms at work that are required for proper PCP establishment *in vivo*.

To date, many direct protein-protein interactions between core PCP proteins have been described, which has led to some understanding of the intracellular regulation of PCP signaling. The C-tail of Fz can interact with the PDZ domain of Dsh *in vitro* (54), and Fz can recruit Dsh to the apical circumference of cells in *Drosophila* (108) and to the cell membrane in cell culture and in *Xenopus* animal cap explants (72, 113–115). On the other hand, Stbm interacts with Pk, and Stbm is required for membrane recruitment of Pk (44, 73, 74, 109). Animal cap recruitment assays have been used to demonstrate a mutual effect between Stbm and Pk on each other's localization. While GFP-Stbm in the absence of exogenous Pk is localized uniformly in the membrane of animal cap cells, addition of Pk leads not only to Pk membrane recruitment, but also to a redistribution of both proteins into clusters within the membrane (44). It is thus plausible that Pk and Stbm have the potential to promote their aggregation into larger protein complexes. One can speculate that, *in vivo*, initial weak differences in PCP signaling can trigger a process of protein separation in a highly organized way (i.e., Fz/Dsh to one and Pk/Stbm to the other end of a cell). This separation could be enhanced by intrinsic aggregation properties of PCP proteins and positive or negative feedback loops (72, 112). In this regard, it has been shown that Pk can interact with Dsh, which probably reduces Dsh membrane localization where Pk concentration is high, thus explaining the inhibitory effect of Pk on Fz-PCP signaling (72).

Dgo has been shown to act positively on Fz signaling in the eye and wing and to colocalize with Fz/Dsh (see above; 43, 69, 105). Dgo can compete with Pk for binding to Dsh and thus prevent the inhibitory action of Pk (43). Furthermore, Dgo membrane recruitment in the eye strictly requires Fz, and co-transfection of Dsh with Dgo (in 293T cells) leads to Dsh phosphorylation. It is thus possible that Dgo stabilizes a complex between Dsh and Fz and thereby increases Fz-PCP signaling activity.

If Stbm/Pk clusters prevent Fz/Dsh complex formation in cis, but promote it on the abutting side in the neighboring cell, there has to be communication across the cellular interfaces. This could be mediated via a soluble relay molecule (factor X; 46, 47) or via a postulated protein-protein interaction between Fz and Stbm (112). However, to date no such interaction has been reported. On the other hand, it has been shown that the atypical cadherin Fmi interacts with itself, mediating a homophilic interaction between neighboring cells (67) and thus could also mediate a "functional" Fz/Stbm interaction. It will therefore be important to test for potential interactions of Fmi with either Fz or Stbm in cis.

The core PCP proteins are not the only factors that are asymmetrically distributed in the apical cellular cortex. The GαO subunit of heterotrimeric G proteins that is required for canonical Wnt and Fz-PCP signaling shows a more diffuse, but still proximally enriched expression pattern (116). Conversely, the B' subunit (Widerborst) of protein phosphatase 2A (PP2A) thought to target PP2A to substrates and thus to confer substrate specificity, localizes to a diffuse distal web of microtubules at the level of apical junctions (16, 117). Apparently, the distal localization of Widerborst precedes the asymmetric localization of the PCP proteins. In the absence of *widerborst* function, PCP proteins remain uniform and show no asymmetric distribution (117). It is not known how the asymmetry of Widerborst is achieved. It is tempting to speculate that PP2A is required to keep Fz in a dephosphorylated state and thus to prevent Fz inactivation by phosphorylation. During PCP establishment in the eye, Fz is selectively activated in the R3 and R4 cell by Par3 (Bazooka), which prevents dPatj and aPKC from phosphorylating and inactivating Fz (118). An asymmetric PP2A mediated dephosphorylation and thus activation of Fz could lead to initial biasing of Fz activity towards the distal end.

PCP Signaling and Ciliary Diseases

Recent publications report potential links of PCP signaling and ciliary diseases (119, 120). The elongation of kidney tubules depends on the alignment of the axis of cell division parallel to the direction of extension of the tubules, and perturbation of the mitotic pattern leads to cystic growth (121). Mutations in the gene coding for Inversin, a component of the primary cilia-basal body complex, are associated with left-right axis defects and severe renal cystic disease in mice (122, 123). In humans, *inversin* mutations result in an infantile form of nephronophthisis (NPHP2; 124). Inversin has been shown to suppress Dsh induced axis duplication in *Xenopus*, a phenotype caused by overactivation of canonical Wnt signaling. On the other hand, Inversin is also required for convergent extension. It has been proposed that Inversin acts as a switch between canonical Wnt/Fz and noncanonical Fz/PCP signaling (119), similar to the related Diversin (125).

Inversin, Diversin and Diego are structurally related and are all composed of N-terminal Ankyrin repeats followed by C-terminal regions of different lengths (69, 122, 123, 125). These C-terminal regions of Dgo and Inv both physically interact with Dsh (43, 119) and both act positively on Fz-PCP signaling (note that *dgo* mutations do not show a phenotype reminiscent of overactivation of canonical Wnt/Fz signaling [69]). Loss of Inversin leads to cystic kidneys (dilated tubules), a phenotype which, in contrast to the left-right axis defects, cannot be prevented by inversin lacking the Dvl binding site (126). It has been proposed that Inversin might be required for oriented cell division and thus correct elongation of renal tubules (127).

The most recent link of PCP signaling with a ciliary disease has been found in Bardet-Biedl syndrome (BBS) (120). BBS is a complex disease associated with—among others—renal dystrophy, reproductive tract abnormalities, polydactyly and weak hearing impairment (120, 128). All eight genes that have been linked to BBS appear to be involved in ciliary and basal body functions (120 and references therein). Interestingly, several knockouts of BBS genes in mice show a misorientation of the stereocilia chevron in the organ of Corti characteristic of abnormal PCP signaling (see above). Furthermore, BBS1 and BBS6 knock-out mice also genetically interact with vangl2 mutants: double heterozygous animals show defects in the orientation of inner ear sensory cilia. Similarly, morpholino oligonucleotide mediated knock-down of zebrafish BBS4 can enhance the convergent extension phenotype of mutations in the *tri* gene, the zebrafish ortholog of *vangl2/stbm*. However, the exact mechanistic link between the BBS or other ciliary proteins and PCP signaling needs to be examined in detail before a direct link between ciliary function and PCP signaling can be established.

Conclusions

In recent years, amazing parallels between PCP signaling in *Drosophila* and vertebrates have been discovered. These parallels include not only Fz and Dsh, but also their interactions with the other regulatory PCP factors and the downstream effectors Rho Kinase and JNK. Thus, this pathway that is so critical for the function of diverse organs is highly conserved. However, many puzzling questions remain to be answered. For example, what is or are the signal(s) that initially break the symmetry? Even though there is evidence from vertebrates that Wnts are important for PCP establishment, it is still unclear what their exact contribution is. Another question that needs to be addressed experimentally is how the atypical cadherins Fat and Ds feed into the Fz-PCP pathway on a mechanistic level. Thus, despite the recent significant leap in our understanding of the process, many more aspects of PCP establishment remain unresolved and will keep the scientific community busy in the future.

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The Modern Surgical Management of Atrial Fibrillation

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Abstract

Atrial fibrillation is the most common arrhythmia disorder. Its incidence is especially high among patients with valvular heart disease. Patients with atrial fibrillation are at a six-fold increased risk of stroke and a two-fold increased risk of mortality. Medical management for rhythm control of patients with atrial fibrillation is suboptimal and no better than simple rate management. However, catheter-based therapies are undergoing intense development. The surgical management of atrial fibrillation has undergone considerable innovation in the last two decades; it is the subject of this review. The "cut-and-sew" Cox-maze III is considered the standard for surgical therapy for atrial fibrillation. More recently, several modifications of the Cox maze lesion set and the development of alternative energy sources to achieve transmural atrial lesions have led to a more simplified maze procedure. This simplified left-sided maze procedure has demonstrated excellent efficacy at intermediate and long-term follow-up. Therefore, the modified maze procedure should be offered to all mitral valve surgery patients and potentially to all cardiac surgery patients with a history of paroxysmal, persistent, or permanent atrial fibrillation.

Key Words: Atrial fibrillation, surgery, maze procedure, cryothermia.

Introduction

ATRIAL FIBRILLATION is the most common arrhythmia disorder, with an estimated prevalence of 2.2 million Americans or 0.4% of the general population, and its prevalence increases with age (1). Patients with atrial fibrillation are at an increased risk for developing left ventricular dysfunction, for stroke and other embolic events caused by atrial thrombi, and for mortality (2, 3). Atrial fibrillation is associated with a 6-fold increased risk of stroke and a nearly two-fold increased risk of mortality (3, 4). Patients with atrial fibrillation following coronary artery bypass graft have a 25% increased risk of mortality (3). Additionally, atrial fibrillation may cause various unpleasant symptoms and adversely impact quality of life.

Comorbid cardiac disease is present in up to 70% of patients with atrial fibrillation. Those cardiac diseases predisposing patients to the development of atrial fibrillation most commonly include hypertension, coronary heart disease, and valvular (particularly mitral) and myocardial diseases (5). Patients with atrial fibrillation as compared with patients in sinus rhythm at the time of mitral valve surgery are at an increased risk of cardiovascular death (6).

For the relief of symptoms, prevention of thrombus and stroke, and the avoidance of left ventricular dysfunction, cardiologists make considerable effort to restore and maintain sinus rhythm in patients with atrial fibrillation. However, as has recently been demonstrated in several large, randomized trials, pharmacologic management of atrial fibrillation is hardly better than simply rate control with appropriate anticoagulation to reduce the risk of thromboembolism (7–9). This situation is largely a consequence of the inadequacies of pharmacologic therapy for the maintenance of sinus rhythm (10).

The prevalence of atrial fibrillation, given the limitations of pharmacological therapy for the maintenance of sinus rhythm (8), has led to the development of alternative, non-pharmacological

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approaches to the management of this disorder, including catheter-based or surgical ablation. This review describes past and contemporary surgical approaches to the management of atrial fibrillation.

Definitions and Pathophysiology

Atrial fibrillation is considered paroxysmal or self-terminating when episodes last less than seven days, usually less than 24 hours (1). It is considered persistent if it fails to terminate and lasts longer than seven days. Persistent atrial fibrillation can be terminated by direct current cardioversion or pharmacologic cardioversion. Atrial fibrillation is considered to be permanent when it is present for more than one year and cardioversion has either not been attempted or has failed.

Atrial fibrillation is believed to arise from enhanced automaticity at one or more rapidly depolarizing foci or result from reentry involving one or more circuits (1). The focal origins of atrial fibrillation, which appear to be more important in patients presenting with paroxysmal atrial fibrillation, have most recently been described by Haissaguerre to occur predominantly in the pulmonary veins (11; Fig. 1). Infrequently, foci may also occur in the right atrium, the superior vena cava, or the coronary sinus (11, 12). The multiple-wavelet hypothesis, first described by Moe (13), proposes a reentrant phenomenon such that fractionation of wave fronts as depolarization propagates through the atria and results in self-perpetuating daughter wavelets. The creation of these wavelets depends on local differences in the refractory period, mass, and conduction velocity within the atria. Such changes evolve in the setting of underlying structural heart disease. The multiple wavelet phenomenon appears to be more important in the genesis of persistent atrial fibrillation.

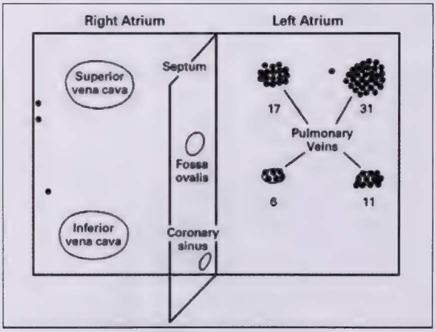

Fig. 1. The source of ectopic foci initiating atrial fibrillation. Reprinted with permission from Haissaguerre, N Engl J Med 1998; 339(10):659 (11).

An understanding of the underlying pathogenesis of atrial fibrillation has been critical in advancing surgical approaches for the treatment of this disorder.

Treatment

An ideal treatment for atrial fibrillation would restore normal sinus rhythm, reestablish atrioventricular synchrony, eliminate thromboembolic risk, and restore atrial transport function. Based on the understanding of the underlying mechanism of atrial fibrillation, several procedures have accomplished these goals to varying degrees. However, the results are limited by the inherent complexity and morbidity associated with the specific procedure.

Medical Therapy

Although details of the medical management of atrial fibrillation are beyond the scope of this review, the tenets of medical therapy include rate control of those patients with persistent atrial fibrillation, using beta-blockers, calcium channel blockers or digoxin, and anticoagulation in those patients at risk for systemic embolization (1). If the decision is made for rhythm control, pharmacologic agents such as flecainide, propafenone, sotalol, and amiodarone may be used, depending on the patient's underlying heart disease (1). However, such medications maintain only 30–60% of patients in normal sinus rhythm at 1–2 years follow-up and have a number of side effects (14). Risk of recurrent atrial fibrillation is dependent on the choice of pharmacological agent and several risk factors for recurrence, including the presence of hypertension, atrial fibrillation for longer than one year, enlarged left atrial size, and left ventricular dysfunction (15).

Catheter-Based Therapy

Atrioventricular nodal ablation. Radiofrequency catheter ablation of the atrioventricular (AV) node can be done in patients with permanent atrial fibrillation for whom pharmacologic therapy is unsuccessful. Because ablation of the AV node causes complete heart block, patients first require implantation of a permanent pacemaker. Nodal ablation is acutely successful in 97% of patients, though up to 3–4% of patients have recurrence of AV conduction at follow-up (16). While AV nodal ablation is highly effective for heart rate control, the left atrium remains in fibrillation so that anticoagulation to prevent systemic embolization, as in patients with chronic atrial fibrillation, remains important.

Pulmonary vein isolation. Based on the surgical experience with atrial fibrillation ablation, a variety of methods of catheter-based radiofrequency ablation are currently being investigated. Current techniques are particularly effective for the treatment of paroxysmal atrial fibrillation (17). Catheter-based ablation has been associated with pulmonary vein stenosis in approximately 5% of patients (18) and on rare occasions has been associated with fatal atrioesophageal fistulas (19). However, as techniques are refined, there is great potential for catheter-based ablation of atrial fibrillation and restoration of sinus rhythm.

Surgical Therapy

Cox-maze III procedure. The Cox-maze III procedure is considered the standard for surgical treatment of atrial fibrillation. Based on experimental evidence of the pathophysiology of atrial fibrillation, Cox designed the initial procedure, then modified it twice, resulting in the Cox-maze III (20, 21). The Cox-maze III operation involves incision and cryolesions designed to interrupt the macroreentrant "wavelet" circuits that characterize persistent atrial fibrillation (Fig. 2). Multiple full-thickness cuts and sutures within the atrial wall disrupt abnormal reentry pathways (22). Both right and left atrial lesions direct sinus depolarization to the AV node. Several "blind alleys" are constructed along the conduction pathway to allow for depolarization of the atria and to enable atrial transport function (20, 21). Additional lesions surrounding the pulmonary veins isolate the potential triggers of atrial fibrillation located in the pulmonary veins. Right atrial lesions are designed to prevent atrial flutter. The Cox-maze III lesion set thus includes: a pulmonary vein isolation lesion, a connecting lesion to the mitral annulus and a connecting lesion to the left atrial appendage, a septal lesion, a cryolesion on the coronary sinus, and a right atrial isthmus lesion (23; Fig. 2). Finally, the left atrial appendage is excised to further prevent thrombus formation. The Cox-maze III procedure is often done in conjunction with operative correction of other structural cardiac abnormalities (24).

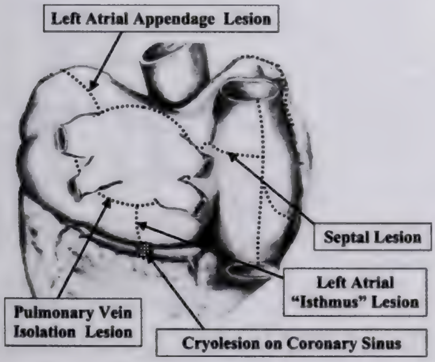
Left Atrial Appendage Lesion
Septal Lesion
Left Atrial "Isthmus" Lesion
Pulmonary Vein Isolation Lesion
Cryolesion on Coronary Sinus

Fig. 2. Lesion set of the Cox-maze III. Reprinted with permission from Cox, Europace 2004; 5 Suppl 1:S20 (23).

The Cox-maze III is remarkably effective and has thus been considered the standard for surgical correction of atrial fibrillation, to which every other procedure has been compared. Freedom from atrial fibrillation has been demonstrated in >95% of patients at 5 year follow-up (25) and >90% of patients at 10 year follow-up (26). Restoration of biatrial transport has been demonstrated in >80% of patients (21). The incidence of stroke is markedly reduced (27). Pacemaker implantation is required postoperatively in 5–10% of patients, though a majority of these are for underlying sinus node disease (28).

However, the Cox-maze III has not been widely adopted as a method for treatment of atrial fibrillation. This is primarily due to the operative complexity of the procedure. Even in experienced hands, the Cox-maze III operation requires about 1 hour on cardiopulmonary bypass (29). Additionally, there may be a high rate of reoperation, following the Cox-maze III, due to bleeding (30).

Modified maze procedure. As an alternative to the Cox-maze III, several new approaches to the surgical ablation of atrial fibrillation have been developed, to decrease the complexity of the surgery while maintaining adequate efficacy. These approaches have been designed around either simpler lesion sets, alternative energy sources to the "cut-and-sew" methodology of the Cox-maze, or an epicardial rather than endocardial application of lesions.

Alternative lesion sets. As the focus of the underlying pathophysiology has shifted to the pulmonary veins, novel approaches focusing on isolating the pulmonary veins from the remainder of the left atrium have been developed. From the work of Alfieri, Mohr, and Melo (30–31), it seems that isolating the pulmonary veins is critical to the success of a modified maze procedure. Additionally, a lesion across the left atrial isthmus connecting the lesions encircling the pulmonary veins to the non-conducting tissue of the mitral annulus is crucial to maintenance of sinus rhythm. In a study of 70 patients with persistent or paroxysmal atrial fibrillation, contiguous lesions surrounding the orifices of the pulmonary veins with a connecting lesion to the mitral annulus resulted in >90% of patients free of atrial fibrillation at 12 months (32). A right atrial isthmus lesion is desirable to prevent postoperative atrial flutter. Finally, as proposed by Cox, a lesion in the coronary sinus is also desirable (23). By eliminating a majority of the lesions and restricting the lesions primarily to the left atrium (34), there is little lost in efficacy, with great reduction in the operative complexity, although there is still controversy about the exact choice of lesion set (29).

Alternative energy sources. While a modification of the lesion set based on a better understanding of the underlying pathophysiology of atrial fibrillation has reduced the operative complexity of the maze procedure, using alternate energy sources such as radiofrequency, cryothermy, microwave, ultrasound, or laser for creating a lesion rather than the traditional "cut-and-sew" method has been the most important advance in the surgical treatment of atrial fibrillation. Using alternative energy sources, operators hope to create transmural atrial lesions analogous to those created with the Cox-maze III. There are potential advantages and disadvantages to each alternative energy source (Table; 35).

Radiofrequency. The largest study experience of alternative ablation technique has been with the use of unipolar radiofrequency catheter systems. Using radiofrequency energy, the probe is heated to 80°C for 1 minute, with consequent coagulation and destruction of cell and collagen structures (22). Endocardial lesion sets of the left or bilateral atria have proven effective in patients undergoing concomitant cardiac surgery, primarily mitral valve surgery (34, 36, 37). In general, the radiofrequency ablation using a flexible probe, rigid probe, or pencil-like probe requires an additional 10–20 minutes of operative time (38, 39). Several case series have demonstrated efficacy of 70–80% freedom from atrial fibrillation (40–42). In a study of 200 patients with permanent atrial fibrillation, Sie et al., using a simplified radiofrequency linear ablation, demonstrated 40-month freedom from atrial fibrillation in 73% of patients, although 49% were on antiarrhythmic drugs (40). As with the Cox-maze III, approximately 10% of patients require pacemakers postoperatively (40).

There are, however, dangers specific to radiofrequency ablation of the left atrium. For example, damage to the circumflex coronary artery and catastrophic atrioesophageal fistula formation have been reported, though these complications are exceedingly rare (32, 43, 44). Additionally, radiofrequency ablation is considered thrombogenic, providing the possibility for postoperative left atrial thrombus formation and subsequent embolic complications (45).

Cryothermy. Unlike radiofrequency ablation, cryoablation generally preserves the integrity of adjacent anatomic structures, due to its preservation of collagen tissue (35). During cryoablation, the probe tip is cooled to –150°C for 1 minute. The freezing and thawing forms intracellular and extracellular ice crystals with resultant irreversible lesions within 2 hours of application (22). Recent molecular-based research suggests that apoptosis may be a mechanism of cell death, particularly in the periphery of the cryogenic lesion (46). By 12 weeks after lesion application, homogeneous, fibrotic, full-thickness lesions of the atrial wall have developed. Additionally, cryoablation is not con-

TABLE

Alternative Energy Sources

	Cryothermy	Radiofrequency	Microwave	Laser
Clinical Experience	Extensive	Extensive	Minimal	Minimal
Endocardial Disruption	Low	High	High	High
Transmural Lesion	Excellent	Limited, Contact dependent	No	No
Perforation	Low	Low	High	High
Thrombogenicity	Low	High	High	High

Adapted with permission from Lustgarten DL, Keane D, Ruskin J. Cryothermal ablation: mechanism of tissue injury and current experience in the treatment of tachyarrhythmias. Prog Cardiovasc Dis 1999; 41(6):481–498 (35).

sidered thrombogenic (35). Several case series have demonstrated similar efficacy of cryoablation and radiofrequency ablation in the management of atrial fibrillation (47–50). Approximately 70–80% of patients remain in sinus rhythm with cryoablation as well. In a study of 95 patients with permanent atrial fibrillation, Manasse et al. demonstrated 81% freedom from atrial fibrillation at 3-year follow-up, with a modified linear cryoablation of the left atrial posterior wall (47). Cryoablation generally requires approximately 10 minutes of operative time (or 20 minutes for biatrial ablation) and currently is done primarily with concomitant cardiac surgery in patients with a history of paroxysmal or persistent atrial fibrillation (50). There have been no reports of collateral coronary or esophageal damage and no reports of thrombus formation.

Microwave. There is considerably less experience with microwave thermal ablation. In this procedure, heat is generated by microwave energy at the probe tip for 20–30 seconds (22). The heating of a microwave probe results in a deep lesion without resultant endocardial char formation, theoretically reducing the risk of thrombus formation (51). Although there is more limited experience, the efficacy seems to be similar to that of radiofrequency or cryothermy ablation, with no reported complications (52–54).

High-frequency ultrasound and laser are additional energy sources that are under ongoing investigation but have not yet come into common clinical practice (51).

Epicardial versus endocardial lesion application. Epicardial lesion application offers several distinct advantages over the endocardial approach. Epicardial application allows for a beating-heart procedure, minimizing cardiac ischemic time and allowing for a less invasive thoracoscopic approach (Fig. 3; 55). In addition, epicardial application affords better handling of anatomic variation of the pulmonary venous trunks and minimizes the risk of pulmonary vein stenosis. Finally, the reported efficacy is similar to that of endocardial alternative lesion approaches with similar operative time (56, 57). Epicardial lesion application has been performed with both radiofrequency and microwave energy (55, 57, 58). Although there have been no reports of esophageal perforation, left main coronary injury has been reported (59).

Predictors of failure. Several series have studied predictors of success or failure when performing a maze procedure during concomitant cardiac surgery. Preoperative decreased amplitude fibrillatory wave, increased left atrial size, and increased cardiothoracic ratio have been predictive of early recurrence of atrial fibrillation in patients undergoing a traditional Cox-maze III procedure (60). The primary predictor of late recurrence in patients undergoing the Cox-maze III is duration of preoperative atrial fibrillation (26). The pathogenesis of the underlying disease was not predictive of Cox maze success (61). However, left atrial size reduction post-operatively was predictive of Cox maze success. Fewer studies have considered predictors of failure of a simplified maze using alternative energy sources. Preoperative increased left atrial size has been predictive of recurrent atrial fibrillation in patients undergoing a simplified radiofrequency maze procedure (36). But these identified factors are probably indicative of more extensive structural heart disease, which leads to the development of wavelet-mediated persistent atrial fibrillation.

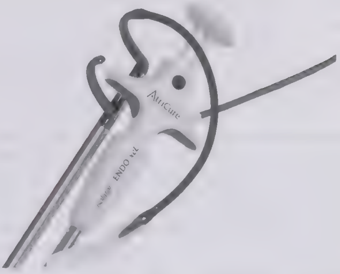

Fig. 3. Bipolar radiofrequency clamp. Reprinted with permission from AtriCure, Inc., Cincinnati, OH.

Left atrial appendage ligation. The left atrial appendage has been implicated as the primary repository of thrombus in patients with atrial fibrillation, particularly non-valvular atrial fibrillation (62). Several studies have tested the feasibility of left atrial appendage obliteration to reduce the risk of stroke (62, 63). However, no large study evaluating this practice has yet been performed. Additionally, there is a risk of incomplete exclusion of the left atrial appendage, which has been reported in as many as 30–40% of patients on postoperative transesophageal echocardiogram (64). Most recently, there has been interest in the feasibility of percutaneous occlusion of the left atrial appendage (65). At this time, left atrial appendage obliteration continues to be a component of the traditional Cox-maze III procedure. There is variability in the practice of left atrial occlusion in patients undergoing a simplified maze procedure, since the benefit has not clearly been shown.

Postoperative management. There is no consensus regarding the postoperative management of patients undergoing a surgical maze procedure. In general, if the patient is in atrial fibrillation at the time of surgery, amiodarone is given in the operating room and continued in the early postoperative period. Anticoagulation is started prior to discharge and continued for at least 3 months. Anticoagulation should be stopped only if a Holter monitor shows no episodes of atrial fibrillation. Temporary pacing wires are placed in the operating room for management of postoperative bradycardia. Patients in the early postoperative period may develop a variety of arrhythmias including atrial fibrillation, atrial flutter, or junctional rhythm. Occasionally patients will require a permanent pacemaker, although the indication is primarily for sinus node dysfunction (66).

The Mount Sinai experience. In a recent review of operative outcomes of the modified maze procedure at Mount Sinai Hospital, we obtained follow-up on 73 consecutive patients. Between January 2002 and August 2004, 73 patients underwent a modified left-sided maze procedure in conjunction with mitral valve surgery. A majority of these patients (87%) underwent mitral valve repair. The initial 23 patients underwent unipolar radiofrequency left-sided maze ablation. Although there were no complications associated with the radiofrequency maze ablation, the energy source was changed to cryothermy because of the reported complications associated with radiofrequency ablation reported in the literature. Subsequently, 50 additional patients underwent a cryothermy left-sided maze ablation. The lesion set consisted of contiguous endocardial lesions surrounding each group of right and left pulmonary veins with an interconnecting lesion between the pulmonary venous ostial lines and a connecting lesion to the posterior segment of the mitral annulus. There were no additional right-sided lesions.

At an average of 342-day follow-up, there were 5 deaths. Similar to the previously described case series, 69% of patients in our series were in normal sinus rhythm at follow-up. Seven percent (7%) of these patients required cardioversion and 14% required antiarrhythmic therapy to maintain sinus rhythm. Seven percent (7%) of patients required a pacemaker implantation postoperatively. One patient had a stroke postoperatively.

Conclusions

Atrial fibrillation is an increasingly prevalent disease that is a burden to our aging population. Improved understanding of the pathogenesis of atrial fibrillation and the development of new technologies based on this understanding have led to a renewed interest in the surgical therapy of atrial fibrillation. The much simplified surgical treatment of atrial fibrillation using a modified maze procedure has been safe and effective thus far, and should therefore be offered to all mitral valve surgery patients with a history of paroxysmal, persistent, or permanent atrial fibrillation. Currently it is the standard of care in our institution. With the development of epicardial atrial fibrillation ablation, the thoracoscopic treatment of atrial fibrillation is a very promising, less invasive treatment option for the near future.

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Cardiovascular Risk in the Spectrum of Type 2 Diabetes Mellitus

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Abstract

The clinical importance of the metabolic syndrome is that this group of risk factors greatly increases the likelihood of cardiovascular events, the major source of disease morbidity and mortality in patients with obesity and type 2 diabetes. Recent studies have helped clarify the mechanisms underlying the vascular dysfunction that leads to cardiovascular outcomes in diabetes. This vascular dysfunction is correlated with visceral adiposity, insulin resistance and alterations in the levels of a variety of circulating factors. The vascular effects of overt hyperglycemia also play an important role in diabetes mellitus. Appropriate management of diabetes in the context of the metabolic syndrome requires that we pay close attention to minimizing cardiovascular risk. In this brief review, we will cover several key concepts in the pathophysiology of type 2 diabetes that confer increased cardiovascular risk and influence the choice of oral therapies for this widespread disorder.

Key Words: Atherosclerosis, myocardial infarction, insulin resistance, obesity, metabolic syndrome, thiazolidinediones, metformin, sulfonylureas.

THE SIGNIFICANCE of the metabolic syndrome to clinicians is that it confers a dramatically increased risk for cardiovascular events (1). The basis of cardiovascular risk in the setting of the metabolic syndrome is related to visceral adiposity, insulin resistance and alterations in the circulating levels of adipose-tissue-derived circulating factors that lead to a matrix of atherogenic processes. These include glycemic disorders leading to type 2 diabetes, a dyslipidemia characterized by low high-density lipoprotein (HDL) cholesterol and small, dense low-density lipoprotein (LDL) particles, as well as hypertriglyceridemia, hypertension, endothelial dysfunction, vascular inflammation and impaired thrombolysis, among other alterations (Table 1). Given the widespread prevalence of this constellation of disorders in the U.S. and other developed countries of the world, the management of diabetes in the context of the metabolic syndrome requires that we pay close attention to minimizing cardiovascular risks.

In this review, we will cover several key concepts in the pathophysiology and management of type 2 diabetes and the risk factors in the metabolic

TABLE 1
Visceral Adiposity Leads to a Network of Atherogenic Factors in the Metabolic Syndrome

Pathogenic Alterations	Disease-State Consequences
Insulin Resistance	Type 2 diabetes and glycemic disorders
↑FFA	Dyslipidemia (low HDL; high triglycerides; small, dense LDL particles)
↑Cytokines (TNFα)	Hypertension
↓Adiponectin	Endothelial dysfunction, vascular inflammation
	Impaired thrombolysis, increased PAI-1 levels

FFA = free fatty acids; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TNFα = tumor necrosis factor α; PAI-1 = plasminogen activator inhibitor-1.

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syndrome. First, we will consider the growing epidemiologic evidence that abnormalities of glycemia contribute to cardiovascular disease and mortality. Second, we will explore how visceral obesity leads to the metabolic syndrome and diabetes, and how these disease processes contribute to cardiovascular risk. Finally, in the context of the pathophysiology of diabetes and preventing its long-term complications, we will briefly discuss the relative benefits and drawbacks of using currently available oral agents in the clinical management of type 2 diabetes.

Contribution of Abnormal Glycemia to Cardiovascular Disease and Mortality

All forms of diabetes, as defined by fasting or post-oral load levels of glucose above a standardized normal range, are well known to be associated with increased risk of microvascular complications such as nephropathy, retinopathy and neuropathy (2). Moreover, major randomized intervention studies in both type 1 diabetes (Diabetes Control and Complications Trial or DCCT) and type 2 diabetes (United Kingdom Prospective Diabetes Study or UKPDS) have clearly shown that lowering the mean glucose level (reducing hemoglobin A1c, or HbA1c) dramatically protects against the microvascular complications of diabetes (3, 4).

A more difficult task has been to decipher from the available clinical data whether interventions that reduce glucose *per se* will have a positive impact on cardiovascular events. The Framingham Heart Study showed that diabetic patients had markedly increased age-adjusted risks for cardiac failure, coronary heart disease, intermittent claudication and total cardiovascular disease and that these risks were much higher than those of the nondiabetic cohort (5). Importantly, this study also pointed out that the increase in risk was significantly greater for diabetic women. Other studies in type 2 diabetes have demonstrated that the incidence of heart attacks in type 2 diabetics is 2–4 times greater than in nondiabetics, and that the risk of myocardial infarction for a diabetic patient may be comparable to the risk for someone without diabetes who has already had a myocardial infarction (6, 7).

From a pathogenic standpoint, what the significance of elevated glucose itself might be in type 2 diabetes mellitus is still not entirely clear, given the multiple factors of the metabolic syndrome that typically accompany the hyperglycemia in patients with type 2 diabetes. Recent work in type 1 diabetes mellitus has suggested that high glucose may contribute directly to atherosclerosis, since a follow-up report to the landmark DCCT trial showed that the intensively treated group had reduced intima-media thickness on carotid ultrasonography compared to the conventionally treated group, suggesting less progression of vascular disease (8). Other epidemiologic data support a link between hyperglycemia and an increased risk of cardiovascular disease. This includes hyperglycemia in the range of "pre-diabetes" in patients with impaired fasting glucose (100–125 mg/dL) or impaired glucose tolerance (140–200 mg/dL at 2 hours following a 75 gm oral glucose tolerance test) (7, 9). An epidemiologic analysis of cross-sectional data from the UKPDS trial showed a strong association for each 1% reduction in glycosylated hemoglobin (HbA1c) with reductions in risk of myocardial infarction in the range of A1c from <6 to 10% (10). A striking relationship between mean glycemia and cardiovascular mortality was shown in the EPIC-Norfolk Study of men not previously known to have diabetes; the relationship extended even into the normal range for A1c, in comparing a group with a mean <5 with a group in the range of 5.1–5.4% (11). Another widely cited example is the Diabetes Epidemiology: Collaborative analysis of Diagnostic Criteria in Europe (DECODE) Study, which showed that for diabetic and non-diabetic individuals a direct link exists between different categories of fasting or post-prandial glucose levels and increased risk of cardiovascular mortality (12). For example, this study showed that patients with impaired fasting glucose had an adjusted hazard ratio of 1.6 compared to normal individuals (Fig. 1).

These considerations have led to the development of clinical guidelines for glycemic control

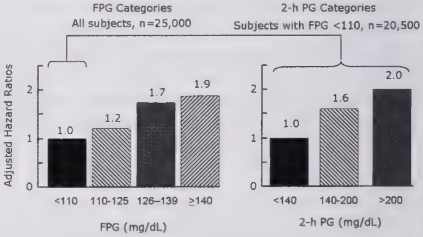

Fig. 1. Fasting plasma glucose and 2-hour plasma glucose post-oral glucose loading predict mortality in persons not known to have type 2 diabetes. Data from the DECODE cohort of 14 European studies with the numbers of patients included (n) shown for each graph. The adjusted hazard ratio for cardiovascular mortality is clearly influenced by either the fasting or post-glucose load category. Adapted with permission from data presented by the DECODE Study Group (12). FPG = fasting plasma glucose; PG = plasma glucose.

based on the prevention of the long-term complications of diabetes (Table 2). The epidemiologic data showing an association of cardiovascular outcomes with the entire range of A1c, even into what is considered "normal," will be further evaluated in several ongoing trials. For example, Action to Control Cardiovascular Risk in Diabetes or ACCORD (www.accordtrial.org) is a large randomized prospective trial to determine whether aggressive glucose control in type 2 diabetes can improve cardiovascular outcomes, supporting the predictions made in the previously cited epidemiologic data.

Pathophysiology of Insulin Resistance and Hyperglycemia in Type 2 Diabetes

Historically, the components of the metabolic syndrome have been linked to an underlying state of insulin resistance, i.e., a reduced biological effect of insulin in the body (13). This underlying insulin resistance leads to compensatory hyperinsulinemia, and at least some of the complex responses that lead to the metabolic syndrome and increase the risk of cardiovascular events. Other pathogenic factors that occur in the syndrome may not be due to effects of hyperinsulinemia or tissue responses that are resistant to insulin itself, but rather to an imbalance in insulin-signaling pathways, some of which remain sensitive to insulin (14). Insulin resistance affects all of the tissues responsive to insulin including the liver, skeletal muscle and adipose tissue (15). In the liver, this leads to ineffective insulin suppression of glucose output, contributing to fasting and steady-state hyperglycemia. In skeletal muscle, inadequate insulin-stimulated glucose disposal also contributes to increased glycemia (Fig. 2).

Among the various adipose tissue depots, expanded visceral fat is especially resistant to insulin, leading to the increased release of free fatty acids. While obesity itself is associated with insulin resistance, it is the central abdominal fat that demonstrates the closest correlation with insulin resistance (16). This study showed that 79% of the variance in insulin sensitivity is associated with central fat regardless of the overall body mass index (BMI). Much recent research has highlighted the role of excess adiposity in causing insulin resistance and type 2 diabetes mellitus, and a better understanding of the underlying mechanisms has begun to emerge (17). By directly interfering with cellular signaling mechanisms, increased levels of fatty acids in the circulation aggravate insulin resistance in skeletal muscle and the liver (18, 19). Increased levels of inflammatory cytokines such as tumor necrosis factor α (TNFα) and interleukin-6 (IL-6) are released by expanded visceral adipose tissue (called "adipokines") and can also adversely influence the insulin signaling cascade (20, 21). These signaling mediators have a detrimental effect on insulin action in liver and skeletal muscle tissue and are believed to contribute to systemic insulin resistance. Interesting

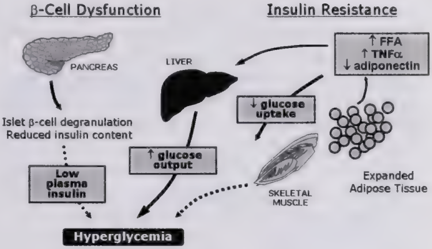

Fig. 2. Insulin resistance and β-cell dysfunction produce hyperglycemia in type 2 diabetes. The pathogenesis of type 2 diabetes is rooted in insulin resistance, with a failure of β-cell insulin secretion to compensate for the increased insulin demands of the body. Recent studies have highlighted the role of an expanded adipose tissue mass, which leads to several pathogenic alterations. Increases are seen in the release of free fatty acids (FFA) and several "adipokines," including tumor necrosis factor α (TNFα), which adversely affects insulin action in skeletal muscle and liver. In addition, levels of the insulin-sensitizing protein adiponectin are increased, which tends to enhance insulin suppression of hepatic glucose production. (See text for further discussion.)

TABLE 2

Current Targets Recommended for Glycemic Control in Clinical Practice

Glycemic Parameter	American Diabetes Association	International Diabetes Federation	American College of Endocrinology
HbA1c (%)	<7.0	≤6.5	≤6.5
Fasting glucose	80–120	<100	<110
2-hour post-meal glucose	–	<135	<140

HbA1c = glycosylated hemoglobin.

recent work has highlighted the close connection between the cellular signaling pathways conferring insulin resistance and classical inflammatory signaling pathways involving the nuclear transcription factor NF-κB (22). High doses of salicylates, which block activation of the NF-κB cascade, can ameliorate insulin resistance and hyperglycemia in diabetes (23). As a common denominator in the cellular action of free fatty acids and various adipokines, the NF-κB pathway appears to be an important target for the development of new therapeutics in insulin resistance, especially in the setting of visceral adiposity.

Increased visceral fat is also associated with accumulation of triglyceride and fatty acid molecules within liver and skeletal muscle cells, which also adversely affects insulin signaling. In susceptible people, the latter may be due to inadequate mitochondrial fat metabolism, which is emerging as a key mechanism leading to intracellular fat accumulation in overfed and sedentary individuals (24).

The adipose-specific secretory protein adiponectin has received much attention recently, since this abundant protein in the bloodstream has insulin-sensitizing effects on liver, muscle and fat tissue as well as anti-inflammatory protective effects on the vasculature (25, 26). Levels of adiponectin are reduced in obese patients with diabetes, and epidemiologic data suggests that it may play a protective role against heart disease in patients with diabetes (27). Interestingly, adiponectin signals via adenosine monophosphate (AMP) kinase, a stress-activated signaling enzyme implicated in a variety of metabolic responses that help to maintain normal glucose metabolism and endothelial function (28). AMP kinase has also been implicated in the mechanism of action of metformin and the thiazolidinediones (TZDs), suggesting that it has a role in clinical anti-diabetic responses (29).

Vascular Endothelial Dysfunction in Type 2 Diabetes and Links to Inflammation

A better understanding of the actions of adiponectin has helped to highlight the pathogenic interconnections between obesity and insulin resistance in metabolic processes as well as on vascular function (25). Early studies showed that patients with type 2 diabetes and insulin resistance had a significantly impaired increase in leg blood flow in response to insulin, suggesting that these patients had defects in endothelial function (Fig. 3; 30). Normal endothelial cells synthesize and release biologically active substances to maintain vascular homeostasis, ensuring adequate blood flow and nutrient delivery while preventing thrombosis and leukocyte diapedesis (31). In insulin-resistant subjects, endothelium-dependent vasodilation is reduced. There appears to be an imbalance between the normal effects of insulin to stimulate nitric oxide (NO) production and vascular dilation, and the growth-promoting effects of insulin that may increase smooth muscle cell proliferation. The insulin resistance in the vasculature arises from the effects of circulating mediators in the endothelium and smooth muscle cells, including free fatty acids, cytokines and adiponectin (25). In overt diabetes, hyperglycemia contributes to endothelial dysfunction and increases vascular oxidative stress (32). Platelet function and plasma coagulation factors are also altered in diabetes, favoring platelet aggregation and a propensity for thrombosis (Fig. 4; 33).

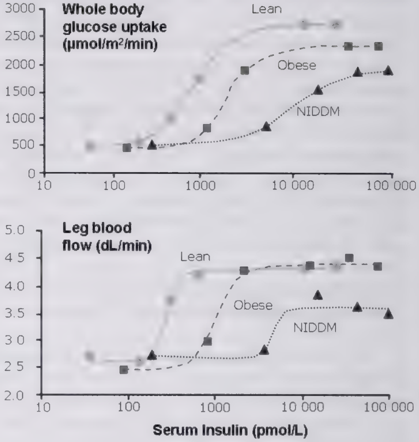

Fig. 3. Insulin resistance and diabetes mellitus impair endothelial function. In lean subjects, obese subjects, and obese subjects with type 2 diabetes (NIDDM), whole body insulin-mediated glucose uptake and leg blood flow in response to insulin were measured. In subjects with diabetes, the response of both measures at maximal insulin infusion was significantly reduced and the sensitivity of these responses to insulin was shifted to a higher dose level. These data show that reduced skeletal muscle blood flow is found in diabetic subjects, and impaired insulin-mediated augmentation of skeletal muscle blood flow is due to the diabetic state *per se* and not to the obesity status. Reproduced with permission from the American Diabetes Association from Laakso et al. (30).

Hyperglycemia in Type 2 Diabetes

Although insulin resistance is typically the first noted defect and is fundamental to the devel-

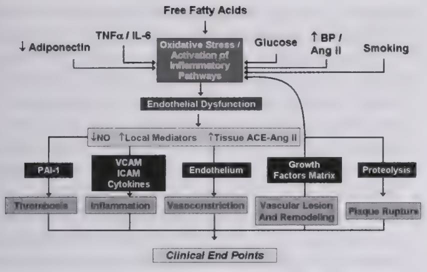

Fig. 4. Mechanisms of vascular injury in insulin resistance and type 2 diabetes mellitus. Many of the same pathogenic factors that cause tissue insulin resistance in glucose and lipid metabolic regulation also lead directly to endothelial dysfunction and increase the risk of atherosclerosis. The array of changes that contribute to type 2 diabetes as well as cardiovascular risk include increases in free fatty acids, tumor necrosis factor α (TNFα), interleukin-6 (IL-6), angiotensin II (Ang II) and glucose, and reduced levels of adiponectin. These factors impact on oxidative stress in vascular tissues and lead to a matrix of alterations that are detrimental to the normal functions of the vascular endothelial and supporting structures. (See text for further discussion.)

BP = blood pressure; PAI-1 = plasminogen activator inhibitor-1; NO = nitrous oxide; ACE = angiotensin-converting enzyme.

opment of type 2 diabetes, if compensatory increases in circulating insulin occur, blood glucose levels can be held in check (Fig. 2). Only with an accompanying failure of β-cell insulin secretion will glucose levels climb, leading to overt diabetes (17). It has been estimated that by the time diabetes is manifest; approximately 50% of β-cell function has been lost (34). Many of the mechanisms in obesity that contribute to tissue defects in insulin action also play a role in the decline in β-cell function in diabetes, including excess circulating free fatty acids, accumulation of triglycerides in the islets and mitochondrial abnormalities (24).

Choosing among Oral Therapies for Type 2 Diabetes

Consideration of the pathogenesis of type 2 diabetes and the role of inflammation and vascular dysfunction as risk factors for the long-term cardiovascular consequences of the disease helps the physician select from among the many available options for oral treatment of this disorder (Fig. 5), once lifestyle modifications have been implemented and found to be insufficient. Our general approach involves the early use of metformin and TZDs, which use the insulin already available in the patient's circulation, and can lower blood glucose without causing hypoglycemia, even when aggressively used in combination to drive the A1c into the normal range (Fig. 6). Since both metformin and TZDs require endogenous insulin to be effective, if these medications do not enable a patient to reach glucose goals, an insulin secretion enhancer should be added. Of course, the secretion enhancers rely on a responsive mass of β-cells, so when this becomes inadequate, insulin itself must be added to the oral agents. The best ways to achieve and maintain glucose goals over the long term include individualization of the therapy and regular review and modifications.

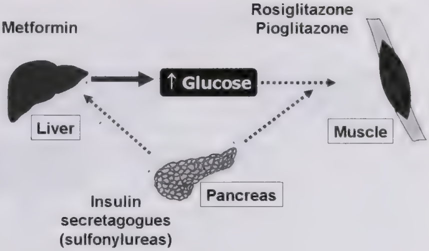

Fig. 5. Sites of action of major oral therapies for type 2 diabetes mellitus. Metformin is thought to act primarily in the liver to suppress hepatic glucose production. The thiazolidinediones (rosiglitazone and pioglitazone) act via an entirely different mechanism that involves an initial interaction with the peroxisome proliferator-activated receptor-γ (PPAR-γ) nuclear receptor in adipose tissue. This causes a redistribution of adipose stores and alterations in the secretion of free fatty acids and several "adipokines," which helps to ameliorate the insulin resistance, primarily in skeletal muscle. Thus, the major effect of the thiazolidinediones is to enhance insulin-stimulated glucose disposal in skeletal muscle. The insulin secretagogues, including the long-acting sulfonylureas and the shorter-acting meglitinide and phenylalanine derivatives (repaglinide and nateglinide), increase insulin secretion from the pancreatic β-cells. (See text for further discussion.)

Metformin and the TZD Class

Metformin and TZDs work independently of the pancreas and help to lower insulin levels by unique mechanisms (35, 36). Metformin is an "insulin-sparing" drug that suppresses hepatic glucose production, while the TZDs affect adipose tissue metabolism in a manner that alters the secretion of free fatty acids and adipokines, and helps to suppress the "inflammatory" milieu that contributes not only to insulin resistance in metabolic tissues but also to vascular dysfunction (14). While metformin has been shown in some studies to produce increases in insulin sensitivity, the TZDs are true insulin-sensitizers that exhibit more potent effects on a number of metabolic syndrome parameters that are associated with insulin resistance (see below).

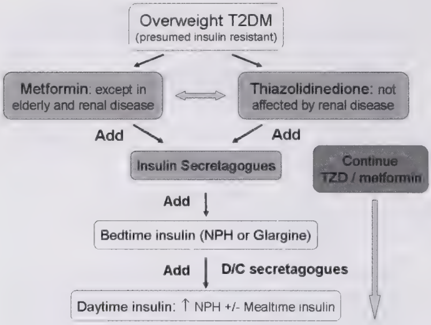
Overweight T2DM
(presumed insulin resistant)
Metformin: except in elderly and renal disease
Thiazolidinedione: not affected by renal disease
Add
Add
Insulin Secretagogues
Continue TZD / metformin
Add
Bedtime insulin (NPH or Glargine)
Add
D/C secretagogues
Daytime insulin: ↑ NPH +/- Mealtime insulin

Fig. 6. General scheme for initiating and intensifying oral therapy in type 2 diabetes. Overweight patients with type 2 diabetes mellitus (T2DM) can be presumed to be insulin resistant, and therapy should be initiated with metformin, with the early addition of a thiazolidinedione (TZD) when necessary. Metformin is strictly contraindicated in renal insufficiency and in many elderly patients with reduced renal function or congestive heart failure, as discussed in the text. One of the benefits of the metformin-thiazolidinedione combination is the lack of hypoglycemia, even with aggressive treatment, since both of these drugs work independently of the pancreas and lower circulating insulin levels. If additional insulin is needed to support the action of metformin and/or thiazolidinediones, a secretion enhancer should be added for "triple" oral therapy. With a failing β-cell mass, as in long-standing diabetes, the secretagogues may not provide an adequate glucose lowering effect, and exogenous insulin is required. Once exogenous insulin therapy is intensified, the oral secretion enhancers should be discontinued (D/C), but since these patients typically remain insulin resistant, thiazolidinediones and/or metformin should be continued in combination with insulin.
NPH = isophane insulin.

Role of Metformin in Cardiovascular Protection

Most of the data supporting a role for metformin in cardiovascular protection arises from a small substudy in which compared to conventional treatment, the intensive use of metformin in obese patients showed a reduction of 36% in all-cause mortality and 39% in myocardial infarction (p=0.01) (37). However, the mechanism of metformin action in regard to reduction of cardiovascular events is not well understood. In a meta-analysis of 32 studies involving more than 2,400 patients, metformin was effective in lowering A1c, but had no significant effect on blood pressure or HDL. Also, the effects on LDL and triglycerides were statistically significant, but small, and felt unlikely to be of major clinical benefit (38). A recent study reported a 16-week interim analysis of metformin vs. placebo as an adjunct to insulin in patients with type 2 diabetes (39). In this study, metformin did not lower albumin excretion or reduce C-reactive protein (CRP) levels, which is unlike the response to TZDs. Metformin did have significant effects on several markers of endothelial and thrombolytic function, including reductions in vascular cell adhesion molecule-1 (VCAM-1), plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA). Additional data from this ongoing trial should help to show potential long-term effects of metformin in these patients.

Metformin has a long record of safety and has been used extensively in Europe for decades. A unique benefit of metformin among oral treatments for diabetes is that it does not cause weight gain, and in combination therapy it helps to limit the weight gain associated with the use of TZDs or sulfonylureas (Table 3). The most common limitations to the use of metformin include intolerance to the drug secondary to its gastrointestinal side effects and the contraindication against using metformin in renal or hepatic insufficiency. Metformin cannot be used by patients with elevated serum creatinine and abnormal creatinine clearance (<60–70 mL/min), or by patients with congestive heart failure requiring pharmacological management, because of the risk of lactic acidosis if the drug is allowed to accumulate. For patients admitted to the hospital for radiological or surgical procedures, metformin should be stopped until the patient fully recovers and then restarted only after the serum creatinine level is checked and demonstrated to be normal (40).

Thiazolidinediones

Just as insulin resistance plays an important role in the development and progression of type 2 diabetes mellitus, the TZD insulin sensitizers ex-

TABLE 3
Metformin in the Management of Type 2 Diabetes Mellitus

Advantages	Disadvantages
Suppresses hepatic glucose production	Gastrointestinal side effects in up to 50%
High initial response rate	Not tolerated in up to 4%
"Insulin-sparing" with rare hypoglycemia	Risk of lactic acidosis in renal insufficiency
Long record of safety	Contraindicated in patients with CHF
Limits weight gain	Twice-daily dosing
Decreased CVD in UKPDS substudy	

CHF = congestive heart failure; CVD = cardiovascular disease.

hibit a variety of biological actions that ameliorate many of the abnormalities and cardiovascular risk factors that accompany type 2 diabetes and the metabolic syndrome (Table 4). At present two TZDs, pioglitazone and rosiglitazone are Food and Drug Administration (FDA) approved for the treatment of type 2 diabetes mellitus. The TZDs act by binding to the nuclear transcription factor peroxisome proliferator-activated receptor (PPAR)-γ, which is found primarily in adipose tissue. The precise mechanism of action of TZDs is still under investigation, but the initial action of these drugs is mediated by effects in adipose tissue, where they modify the fat distribution in the body, reduce tissue accumulation of triglycerides and alter the secretion of adipokines in a manner that ameliorates the latter's influence on insulin resistance and vascular endothelial function. Levels of adiponectin increase and levels of pro-inflammatory cytokines decrease (36, 41). The TZDs also have direct anti-atherosclerotic effects on the vascular wall and anti-inflammatory effects on circulating leukocytes.

The TZDs exert beneficial effects on the dyslipidemia of type 2 diabetes, increasing HDL cholesterol and reducing LDL particle density, and tend to reduce triglycerides (42). Although the mechanisms of these effects are not entirely understood, they may arise from an improvement in the underlying insulin resistance and changes in lipid transfer proteins and hepatic lipase. Microalbuminuria is a cardiovascular risk marker that is believed to represent not only glomerular leakage, but also systemic endothelial dysfunction and permeability (43). TZDs as a class are associated with a reduction in microalbuminuria in type 2 diabetics independent of reductions in glycemia or blood pressure. Most likely, this effect of TZDs is a reflection of their vascular protective properties, which may also translate to a decrease in the cardiovascular risk (44). Acting via the PPAR-γ mechanism, the TZDs also ameliorate several "non-traditional" cardiovascular risk factors and inflammatory mediators, including CRP, IL-6, matrix metalloproteinase-9 (MMP-9), and the leukocyte count (45, 46). As a summation of the many and varied effects of TZDs in the vasculature, endothelial functions are improved by treatment with TZDs, as assessed by brachial artery reactivity (47, 48). And by enhancing endothelial function and NO availability, the TZDs have also been shown to have a favorable effect on blood pressure in diabetic individuals. In one study, addition of rosiglitazone in patients taking sulfonylureas who had equivalent glycemic control after 1 year was associated with significant reduction of both systolic and diastolic blood pressures in the rosiglitazone group (49).

TABLE 4

Thiazolidinediones in the Management of Type 2 Diabetes Mellitus

Advantages	Disadvantages
Acts *via* PPAR-γ in adipose tissue with secondary effects in skeletal muscle and vascular cells	Delayed onset of action
Insulin sensitizer—no hypoglycemia	Weight gain common
Safe in renal insufficiency	Fluid retention possible with rare episodes of CHF
Evidence for preserved β-cell function	
Various protective vascular effects	
Positive lipid effects	

PPAR-γ = peroxisome proliferator-activated receptor-γ; CHF = congestive heart failure.

Insulin Secretagogues

Before the re-introduction of metformin in the U.S. and the availability of TZDs, insulin secretagogues were the mainstay of oral treatment for the management of type 2 diabetes (Table 5). The long-acting sulfonylureas and the shorter-acting prandial secretion enhancers (meglitinides) are still in use, although most of the treatment guidelines for type 2 diabetes place them at least second to metformin, and some guidelines suggest using the secretagogues third in line after TZDs. This suggested ordering of the introduction of oral therapies for type 2 diabetes mellitus takes into account our current understanding of the pathophysiology of insulin resistance in diabetes and its intimate relation to the risk of cardiovascular disease. Perhaps the most important consid-

TABLE 5

Insulin Secretion Enhancers in the Management of Type 2 Diabetes Mellitus

Advantages	Disadvantages
Increases β-cell insulin secretion	No insulin sensitization or vascular effects
High initial response rate	Hypoglycemia common with aggressive dosing
No lag time	May exacerbate visceral fat accumulation
Once-a-day or multiple dosing schemes possible	May worsen progressive loss of β-cell function
Least expensive	

eration is that, unlike metformin and the TZDs, the sulfonylureas have not shown any significant protective role against the development of cardiovascular disease.

When additional insulin is needed to control blood glucose, insulin secretion enhancers are effective in triggering insulin release from the pancreas, as long as the β-cell mass in the pancreas remains responsive. In patients with long-standing diabetes, loss of β-cell responsiveness may preclude a clinical benefit from sulfonylureas and necessitate insulin injections (50).

Combination Therapies

One of the most important lessons of the UKPDS is the realization that patients with type 2 diabetes endure a progressive loss of β-cell secretory capacity, which necessitates the use of combination therapy, often within a few years of diabetes diagnosis. The general acceptance of tight glucose goals has also led to the need for earlier adoption of combination oral therapies. The combination of a TZD with metformin in the early stages of diabetes appears to be among the best approaches available. These two agents can help ameliorate both insulin resistance and hyperinsulinemia, along with many of the disease manifestations that accompany this pathogenic condition. Importantly, the use of combination TZD and metformin can help to achieve glucose goals without causing hypoglycemia, which is a frequent side effect an insulin secretion enhancer.

When additional insulin secretion is needed, sulfonylureas can be efficacious in combination with TZDs or metformin. In one recent 2-year study of an elderly cohort of patients with type 2 diabetes with mildly elevated A1c (~7.5%), the addition of rosiglitazone to half-maximal sulfonylurea therapy was well tolerated and resulted in about half of the patients achieving A1c below the American Diabetes Association target of 7%. Interestingly, although fluid retention with the TZD class has been observed to be potentially increased in combination with sulfonylureas, in this study patients had a 9–10% incidence of edema at baseline, and while there were more patients with edema in the rosiglitazone-treated group than expected, only 2 patients withdrew from the study due to edema, and there were no cases of congestive heart failure (51).

In keeping with an attempt to achieve aggressive glucose goals, many patients require treatment with each of the three major modalities of oral therapy, i.e., triple oral therapy. Studies have typically shown that patients adding a TZD to their regimen of metformin and a sulfonylurea can expect to have an additional 0.7–1.0% drop in their hemoglobin A1c (52). The use of triple oral therapy should therefore be considered prior to adding insulin, in order to achieve glucose goals in type 2 diabetes.

Conclusions

Diabetes and obesity are widespread conditions with major implications in the modern world and an increasing burden for developing societies. Controlling the long-term complications of diabetes will go a long way toward ameliorating patient morbidity, and mortality, as well as helping to defray costs of medical care and lost time from employment. As a core defect in type 2 diabetes mellitus and a source of cardiovascular risk in the metabolic syndrome, insulin resistance must be addressed in any initial treatment strategy and attention should be paid to it throughout the course of type 2 diabetes. One of the best ways to improve insulin resistance is through lifestyle changes, reduction of body weight and exercise, although this approach frequently fails over the long term. Since most patients need medications in the course of managing their diabetes, this review has outlined a rationale for initiating therapy aimed at cardiovascular risk and insulin resistance by using metformin with the early addition of a TZD. Since the secretion enhancers do not offer any specific protection from cardiovascular risk, their use should be delayed until the patient requires supplemental insulin for the best therapeutic benefit from metformin and the TZDs, even in combination as "triple therapy." Although beyond the scope of this review, when insulin is required to achieve glucose goals, the clinician should bear in mind that, even when insulin deficient, most patients with type 2 diabetes remain insulin resistant, and the insulin should be added to ongoing therapy with either metformin or in combination with TZDs as well. Patients should be helped to achieve glucose goals, including HbA1c of less than 6.5–7.0%, and to gain control of other major cardiovascular risk factors, including lipids and blood pressure. The clear demonstration of improved patient outcomes by paying attention to various cardiovascular risk factors and glucose control, as shown in the Steno 2 study (53) and others, firmly supports this approach to protecting patients from the devastating consequences of this all-too-common disorder.

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Phenotypic Diversity in Delayed Drug Hypersensitivity:

An Immunologic Explanation

Marc J. Meth, M.D., and Kirk E. Sperber, M.D.

Abstract

Drug hypersensitivity reactions are a significant cause of iatrogenic-induced illness. (They were originally classified as type IV hypersensitivity, to describe the tuberculin skin reaction.) It now appears that the T-cell directs the entire inflammatory cascade induced by delayed drug allergy. Delayed drug hypersensitivity, usually manifested in the skin, is triggered when drug-specific CD4+ and CD8+ T cells recognize drugs through their T-cell receptors in a process that is dependent on a major histocompatibility complex. Drugs stimulate T-cell receptors by either covalently binding to peptides or using their structural features to interact via a more direct approach. Immunohistochemical and functional analysis of drug-reactive T-cell clones has shown that the phenotypic pattern of delayed drug hypersensitivity depends on the cytokine pattern induced. For example, maculo-papular exanthema may be either TH-1 or TH-2 in nature, depending on whether they are interferon-γ/tumor necrosis factor-α or interleukin-4, 5 and 13 driven. Bullous reactions to drugs (i.e., Stevens-Johnson syndrome or toxic epidermal necrolysis) are characterized by widespread keratinocyte apoptosis, a consequence of high CD8+ T-cell involvement and the molecular cytotoxicity of Fas, perforin and granzyme B. Pustular exanthema reactions to medications are stimulated via the T-cell release of IL-8 and granulocyte-monocyte colony-stimulating factor (GM-CSF). With better understanding of these unique inflammatory cascades, delayed type IV hypersensitivity reactions have been re-classified into four main subtypes: IVa (TH-1/monocyte directed), IVb (TH-2/eosinophil directed), IVc (CD8+/ Fas/perforin/Granzyme B directed) and IVd (IL-8/GM-CSF/neutrophil directed). Clinically, delayed hypersensitivity eruptions are often an overlap of cytokine pathways, with one preferential reaction dominating the final picture.

Key Words: Drug hypersensitivity, allergy, T-cell, type IV reaction.

Introduction

Adverse reactions to medications are among the leading causes of iatrogenic morbidity and mortality. Most adverse drug reactions (ADRs) result from the predictable and pharmacological effects of the drug itself (type A reactions), but many do not and are instead immune mediated (type B). These drug hypersensitivity reactions are responsible for more than 14% (1) of all ADRs, with manifestations ranging from morbilliform and bullous exanthema to anaphylaxis. Their frequency is highly drug dependent (i.e., such drugs as antibiotics and anticonvulsants [2]), with cutaneous sequelae being the most common complication (1, 3). Adverse cutaneous reactions to medications affect some 2–3% of all hospitalized patients (3).

Despite uncertainty as to the pathophysiology of drug hypersensitivity, these reactions have nevertheless been categorized in a way that correlates clinical findings with the immunological mechanism involved. This classification scheme, as first described by Coombs and Gell (4), groups drug hypersensitivity and immune mechanisms into four main types. Type I reactions are mediated by immunoglobulin E (IgE), as a result of which antigens trigger mast cells and basophils to release substances that may induce urticaria, bronchospasm and anaphylaxis. Type II reactions are elicited by IgG-mediated cytotoxic mechanisms, which are responsible for hemolytic anemia, thrombocytopenia, Graves disease and myasthenia gravis. Type III reactions are immune-complex mediated (e.g., vasculitis secondary to hepatitis B and C infection). Type IV or delayed hypersensi-

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tivity reactions (originally used to describe the tuberculin skin reaction) represent the clinical outcomes that are T-cell mediated.

While the Coombs and Gell classification system has proven useful in clinical practice, new research has shown it to be too simplistic, especially in terms of delayed hypersensitivity. Instead, the T-cell response is far more heterogeneous than previously thought, as clearly reflected in the varied manifestations of type IV reactions. *In vitro* and *in vivo* studies have demonstrated that different cytokine and chemokine patterns produced by T cells (e.g., CD4+ TH-1/TH-2) are responsible for this phenotypic diversity (5, 6). TH-1 T-cell responses are induced by interferon (IFN)-γ and interleukin (IL)-2 while TH-2 T cells produce IL-4 and IL-5. Depending on the involvement of cytokines such as IL-4, INF-γ, and granulocyte-monocyte colony-stimulating factor (GM-CSF), different effector cells (i.e., macrophages, neutrophils, T cells) are induced to mediate a unique inflammatory response. CD8+ T cells have shown similar ability to produce polarized patterns of cytokines involved in the type IV reaction. The clinical picture of delayed hypersensitivity is therefore now understood to be dependent on the cytokine profiles of the T cells. Recognizing this heterogeneity of T-cell function, immunologists have re-categorized delayed hypersensitivity into type IVa, type IVb, type IVc, and type IVd reactions (7). Types IVa, IVb, and IVc correspond to TH1, TH2, and cytotoxic reactions, while type IVd refers to the IL-8 driven response seen in pustular exanthemas such as acute generalized exanthemata pustulosis (AGEP) and Behçet's disease.

This review will describe the most current understanding of the T cell's role in delayed drug hypersensitivity. While this role was once seen as fairly straightforward, both functional and immunohistologic analyses of different peripheral blood T-cell clones present in drug-allergic patients have allowed us to view the type IV reactions as far more complex than was first thought (8–10). We now understand that the clinical presentation of a delayed hypersensitivity reaction depends on the T cells and cytokine pathways involved, a finding with profound clinical implications. Deeper insight into the molecular pathophysiology of type IV hypersensitivity should bring about better treatment and preventative strategies for those who suffer from these reactions.

Initiating the T-Cell Response

Despite recent discoveries, the T cell's role in drug hypersensitivity has been slow to emerge. Initially associated with reactions to tuberculin, hypersensitivity mechanisms are utilized in patch testing. *In vitro* analysis of both skin and blood has proven T cells to be involved in delayed hypersensitivity reactions ranging from dermatitis to systemic eosinophilia and hepatitis (11–13).

Delayed hypersensitivity reactions are initiated by an interaction between T-cell receptors (TCRs) and processed antigens on antigen-presenting cells (APCs) like macrophages, dendritic cells and B cells. Each human T cell displays thousands of identical TCRs, which are heterodimers of two chains, designated as either $\alpha\beta$ (the majority) or $\gamma\delta$ (5% of all T cells). TCRs on CD4 T cells are activated when APCs present immunogenic peptides in the context of a major histocompatibility complex (MHC) class II molecule and co-stimulatory molecules (CD80 and CD86). In contrast to CD4 T cells, CD8+ T-cells are stimulated through interaction of their T-cell receptors with antigens presented via MHC class I molecules. MHC I molecules differ from MHC II not only in the type of antigen presented (peptides derived from proteins synthesized and degraded in APC cytosol vs. exogenous protein processed in endocytic vesicles), but also in the type of cellular response induced (cytotoxic vs. "helper/regulatory"). These responses are all mediated via differing cytokine profiles.

It has recently been demonstrated that T-cell receptors must have clear specificity for different drugs. Molecular analysis of T-cell clones involved in both cutaneous and hepatic delayed hypersensitivity reactions has shown specificity for drugs ranging from antibiotics to anti-convulsants (14–17). These reactions occur because of the enormous variety (greater than 10^7) of TCRs with distinct specificities, which are generated in the neonatal thymus. It is the function of these drug-specific T cells that then determines the clinical pattern of a particular disease (i.e., CD4+ vs. CD8+).

There has recently been extensive research exploring how drugs are recognized by the body. The traditional explanation for how B and T cells identify small, low-molecular-weight compounds such as drugs is referred to as the "hapten" concept. Drugs, unable to mount an immunological response by themselves, become chemically reactive by covalently binding to a larger protein or peptide (18, 19). This "hapten-peptide" subsequently becomes immunogenic when presented to T cells by APCs. Haptens may bind directly to immunogenic peptides attached to MHC molecules or they may alter MHC molecules directly in initiating this response (10, 20, 21). Penicillin G is the typical hapten used to explain such reactions (22). If the drug is not chemically reactive itself, it may *become* reactive during metabolism—representing a "prohapten" (9, 10, 23, 24). The typical example here is that of sulfamethoxazole, which has been shown to be intracellularly metabolized by both hepatocytes (via cytochrome P450) (21, 25, 26) and epidermal keratinocytes before interacting with peptides to stimulate T-cell activation and delayed hypersensitivity (20).

Recently, Pichler's Swiss group has hypothesized a third model to explain drug-T-cell interaction. This model, known as the "p-i concept"—for the "direct pharmacological interaction of drugs with immune receptors"—states that certain drugs are able to bind TCRs and MHC molecules in a direct, non-modified manner (27). According to the "p-i" model, which is both metabolism- and processing-independent, the drug's structural features initiate an immunological response (Fig. 1; 27). This concept was developed because T-cell clones can proliferate in the absence of antigen processing, in contrast to the "hapten" or "pro-hapten" models. T cells can react almost immediately after encountering drugs in the presence of APCs, before any type of intermediate metabolism and processing step can take place (28). There are some antigen-presenting cells that are able to stimulate T cells without the ability to process (29). Additionally, the "p-i" concept offers the only plausible explanation for the many delayed T-cell reactions that are caused by drugs which are either chemically inert or without known metabolism (30, 31). It is postulated that the clinical outcomes of drug reactions may indeed depend on whether the reaction's immunogenicity is chemically ("hapten") or structurally ("p-i") mediated (32). For example, if a drug is immunogenic only by its ability to fit into some TCR, then it may be restricted to T-cell responses, unlike penicillin, which can activate both the T and B cell.

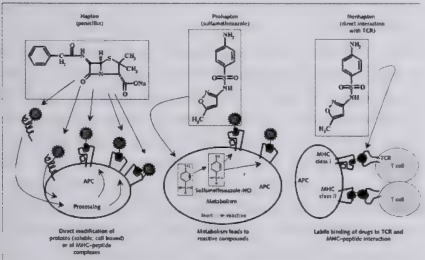


Fig. 1. The hapten, prohapten and direct models of drug presentation to T cells. Reproduced with permission by American College of Physicians: Pichler WJ. Pharmacological interaction of drugs with antigen-specific immune receptors: the p-i concept. Curr Opin Allergy Clin Immunol 2002; 2(4):301–305.
APC = antigen-presenting cell; MHC = major histocompatibility complex; TCR = T-cell receptor.

Whether there is a genetic component to delayed drug hypersensitivity is another question that has been extensively studied. While there are data to suggest an association with certain human leukocyte antigen (HLA) alleles and MHCs (e.g., abacavir with HLA B-*57 [33]), there is little evidence to prove a wider genetic role in type IV reactions (34). It is also unknown whether those genes found are indeed the predisposing factors, or are instead in linkage disequilibrium with the more relevant genes nearby. Additionally unknown is the role of tissue-specific genes, i.e., why delayed hypersensitivity responses are preferentially manifested in one organ as opposed to others.

Cutaneous Manifestations of Delayed Hypersensitivity: Explaining Phenotypic Diversity

Maculo-papular Exanthema

The most common manifestation of an allergic reaction to a medication is a non-urticarial rash. The clinical presentation of these "drug eruptions" is highly variable, ranging from a benign and transient erythema that occurs approximately one week after drug introduction in 1–3% of users (35), to the severest forms (i.e., Stevens-Johnson syndrome or toxic epidermal necrolysis) that affect fewer than one in ten thousand users. It is believed that skin is the most frequent target of delayed hypersensitivity because it is a border region where the immune system is chronically activated to defend the body's integrity. This constant level of low activation provides the medium to facilitate a pro-inflammatory signal and subsequent allergic immune response (36). Mechanistically, the inflammatory cascade is understood to occur via one of two pathways—either the *in situ* activation of local drug-specific lymphocytes (37) or secondary infiltration from distant sites by T cells which express the skin-homing cutaneous lymphocyte-associated (CLA) antigen receptor (38).

Delayed cutaneous exanthema reactions to drugs comprise a broad spectrum of clinical and distinct histopathologic features. Moreover, these reactions have recently been understood not only to vary in presentation, but also to depend upon different cytokine patterns induced. The two most distinct rashes, with differing immune pathogenesis and prognosis, are the morbilliform (or maculo-papular) and bullous types. Maculo-papular rashes are the most common ADRs to affect the skin, accounting for over 90% of all ADRs in some prospective cohort studies (39; Table). They typically begin 4–14 days after drug introduction (even sooner in re-challenges), and can even develop 1–2 days after the patient has discontinued the drug. Morbilliform rashes completely resolve within 1–2 weeks after discontinuing the offending medication. The eruption consists of erythematous macules and/or papules, begins on the trunk and upper extremities, and is frequently symmetric. Pruritis and low-grade fevers often appear with the eruption, usually disappearing in a few days. Histopathologic analysis of maculo-papular exanthema shows a superficial, mainly perivascular, mild-to-moderate mononuclear infiltrate with mild eosinophilia. Microscopically, affected skin may even appear normal. Immunohistochemically, the mononuclear infiltrate is characterized by an accumulation of CD3+ T cells (40–70%) with a clear CD4+ predominance (40–42). CD4+ T cells are predominantly located perivascularly in the dermis, while both CD4+ and CD8+ T cells are equally distributed at the dermoepidermal junction zone adjacent to basal keratinocytes, which occasionally undergo hydropic degeneration (41, 43, 44).

The T-cell infiltrate of maculo-papular eruptions is highly activated, expressing not only the α chain of the IL-2 receptor and HLA-DR, but adhesion molecules like the leukocyte function-related antigen 1 (LFA-1) and L-selectin. Resident cells such as endothelial cells are also activated, expressing the adhesion molecules E- and P-selectin, platelet endothelial cell adhesion molecule 1, and intercellular adhesion molecule-1 (41, 44). MHC class II molecules have also been found on the infiltrate's epidermal cells, both on the residual dendritic cells and on keratinocytes. These keratinocytes are therefore likely not only to be stimulated in morbilliform rashes, but also to present antigen as APCs (41, 44).

TABLE

Drugs that Commonly Induce Delayed Drug Hypersensitivity

Sulfonamides
Aminopenicillins
Radiocontrast media
NSAIDs
Cephalosporins
Phenytoin
Fluoroquinolones
Tetracyclines
Macrolides
Allopurinol
Valproic acid
Carbamazepine
Lamotrigine
Rituximab
Imatinib

While all maculo-papular exanthemas share certain common features, the clinical pattern depends on the type of cytokine profile that is induced. When these reactions are TH-1 driven, INF-γ, IL-2 and tumor necrosis factor (TNF)-α promote the macrophage-induced rash seen in the delayed tuberculin skin response and fixed drug eruptions (5, 45). Much more frequently, they are TH-2 driven, containing mostly CD4+ T cells (with a low number of CD8+ cells), which produce IL-4, 5 and 13 (5, 10, 31). Yawalkar et al. found IL-5s role to be of particular significance in a series of maculo-papular skin biopsies (40). IL-5 serves its function by regulating the growth, differentiation, and activation of eosinophils that are regularly found in the TH-2 pathway (46). There is also evidence that the recruitment and activation of eosinophils may be stimulated by the signaling of chemokines eotaxin and RANTES (regulated upon activation, normal T cell expressed and secreted), which have similarly been found in morbilliform eruptions (40). More than simply regulatory in nature, CD4+ T cells also have the potential to be cytotoxic, responsible for the severest forms of maculo-papular rashes (6, 41). The mechanisms by which these reactions take place are discussed in the following section.

Bullous Exanthema

Bullous exanthemas are grouped on a continuum ranging from erythema multiforme to the Stevens-Johnson syndrome (SJS) to toxic epidermal necrolysis (TEN). By definition, SJS is characterized by bullae (<10% body surface) and necrotic areas of two or more mucosal sites, while TEN involves over 30% of body surface area. Areas between 10–30% represent SJS-TEN overlap. Even though erythema multiforme has recently been categorized as a distinct entity—often triggered by herpes simplex virus or *Mycoplasma pneumoniae* infections and only rarely associated with drug hypersensitivity (47)—SJS and TEN are still among the most dramatic and dangerous consequences of drug therapy. A diagnosis of TEN—incidence of 0.4–1.2 cases per million person-years (48)—continues to have a mortality rate of at least 30%.

The histopathologic features of mild bullous eruptions are actually quite similar to those found in maculo-papular exanthema. They too feature T-cell infiltration, MHC upregulation of keratinocytes and migrating T cells, and focal IL-5 expression (42). Where they differ is that bullous exanthemas contain a much higher percentage of perforin-positive CD8+ T killer cells in both the epidermis and dermis. These killer cells are probably the cause of bullae formation, since they attack not only MHC class II-bearing keratinocytes but also those that express MHC class I (6, 49). All keratinocytes express MHC I molecules on their cell membrane surfaces, like any other nucleated cell, explaining their susceptibility to CD8+ cytotoxic attack.

The reason for the histopathology of the severer bullous eruptions is unclear. Microscopically, SJS and TEN are characterized by full-thickness epidermal necrosis and widespread keratinocyte apoptosis (50). There is only a mild cellular infiltrate in which macrophages and dendrocytes predominate, with a strong immunoreactivity for TNF-α (51). CD4+ T cells predominate in the dermis, while CD8+ cells predominate both at the dermoepidermal junction and in the epidermis (52). It was originally suggested that the apoptosis seen in TEN was mediated by Fas ligand, a soluble molecule of the TNF family that binds to keratinocytes via the Fas "death" receptor. Viard et al. not only showed an upregulation of Fas ligand on affected keratinocytes with TEN, but also attempted to prove that intravenous immunoglobulin (IVIG) had a therapeutic role in treating the disease by its Fas-blocking antibodies (53). It was inferred from their work that keratinocytes that overexpressed Fas ligand could kill neighboring cells that constitutively expressed Fas. Abe et al. showed that serum-soluble Fas ligand secreted by blood lymphocytes and not keratinocytes played the crucial role in Fas-receptor stimulation and thus SJS and TEN (54).

More recently, though, evidence that early bullae in TEN contain an increased number of CD8+ lymphocytes with some natural killer cell-like features, suggests that a contact-mediated killing mechanism may also be involved in SJS/TEN pathogenesis (55). This hypothesis has been borne out through the work of Nassif et al., who have analyzed the bullae of TEN-affected individuals. These bullae have not only contained drug-specific CD8+ lymphocytes, but more important, have shown immunoreactivity for perforin and granzyme B, which can mediate cytotoxicity (56, 57). In spite of our knowledge of the apoptotic and cytotoxic nature of bullous eruptions, the pathogenic mechanisms are still not clear. In fact, there are probably two major pathways involved: that of granule-mediated exocytosis via perforin and granzyme B *and* Fas/FasL interaction. Posadas et al. suggested that there may even be an association between disease severity and perforin/granzyme B levels (58).

Pustular Exanthema

An acute, generalized exanthematous pustule (AGEP) represents the third type of skin eruption found in delayed hypersensitivity, the pustular disorders. AGEP is characterized by numerous small, mostly non-follicular, sterile pustules on a widespread erythematous, edematous base, with an estimated incidence comparable to that of SJS and TEN combined (59). The pustules are mostly confined to the neck, axillae, trunk and upper extremities, and are associated with fever and a leukocytosis. The involvement of drug-specific T cells has been confirmed by patch testing (60, 61). Histopathologically, AGEP reveals spongiform pustules under the stratum corneum. Papillar dermal edema and perivascular polymorphous infiltrate are often also present. On immunohistochemical staining, AGEP's intraepidermal pustules are filled with neutrophilic leukocytes and surrounded by activated HLA-DR-expressing CD4+ and CD8+ lymphocytes. Analysis of cytokine/chemokine profiles has shown that IL-8 is preferentially expressed by keratinocytes and monocytes, encouraging this unique neutrophil-led inflammatory response (61). In addition, the T cells produce high levels of GM-CSF, which is probably important for the survival of the immigrating leukocytes (61).

Systemic Sequelae of Delayed Hypersensitivity: The DRESS Syndrome

When delayed hypersensitivity to drugs extends beyond the skin, it is known as the drug eruption with eosinophilia and systemic symptoms (DRESS) syndrome. First described in a reaction to phenytoin in 1938 (62), it is defined by the triad of fever, skin eruption and internal organ involvement. DRESS usually occurs 1–8 weeks after starting treatment with the inciting drug, and most commonly affects the liver, kidney and lymph nodes. It may have a protracted clinical course, with a mortality rate approaching 10%. Among the most frequent inciting agents are anticonvulsants, allopurinol and sulfonamides (63).

While it was originally believed that systemic delayed hypersensitivity was caused by reactive drug metabolites, *in vitro* analysis of several patients with DRESS syndrome has confirmed the reaction to instead be T-cell mediated (64). To date, T-cell clones have been made specific for lamotrigine and carbamazepine (15, 16). The histopathology of DRESS lesions demonstrates a dense lymphocytic infiltrate in the superficial dermis and perivascular areas, associated with eosinophilia and edema. Immunohistochemically, the eosinophilia appears to be mediated by the lymphocytic production of both eotaxin and IL-5 (40, 65).

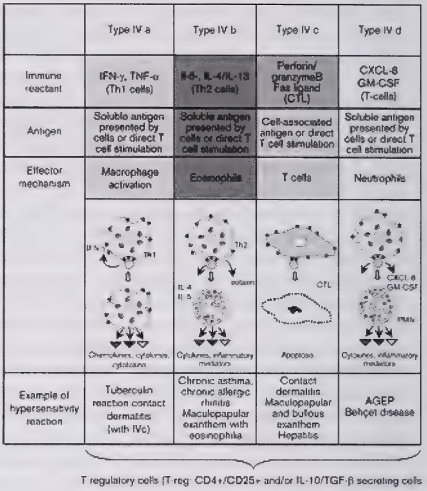
Confirming and Preventing Delayed Hypersensitivity: The Role of Patch Testing

Just as important as understanding the clinical features and pathophysiology of type IV reactions, is knowledge of how to confirm their diagnosis and prevent their recurrence. While clinical history and suspicion will probably make the explanation for a drug eruption obvious in a majority of cases, cutaneous patch testing may prove a useful adjunct (66). Similarly T-cell mediated, patch testing provides a controlled view of delayed hypersensitivity without the risks of systemic absorption. Unfortunately, the overall sensitivity of patch testing is estimated to be approximately 30–60%, meaning that a negative patch test neither excludes nor predicts a hypersensitivity reaction. It appears that the sensitivity of these tests also depends not only on the severity and type of reaction (e.g., patch testing in AGEP is much more sensitive than in SJS/TEN [10, 67]), but on the drug used. The only certain way to confirm and predict type IV hypersensitivity is still to re-challenge, a task both technically difficult for delayed reactions and inappropriate for severe drug reactions (68).

Conclusions

Delayed hypersensitivity reactions to medications have proven to be much more complex than Coombs and Gell first perceived. Dependent on the outcome of varying cytokine pathways, type IV reactions are both extremely diverse and intricate. Various drug hypersensitivity diseases can now be categorized according to the preferential activation of drug-specific T cells with distinct functions (see Fig. 2—immune reactions type IV a–d; 2, 7). To summarize, type IVa hypersensitivity involves TH-1-mediated reactions associated with high IFN-γ production and monocyte activation, while type IVb involves a TH-2-driven IL-4, 5 and 13 eosinophilic response. The Fas/perforin/granzyme B cytotoxicity characteristic of SJS/TEN exanthema makes up type IVc, and the IL-8/GM-CSF neutrophilic response of AGEP defines type IVd. But given these differences, eruptions are often clinically an overlap of the aforementioned pathways, with one preferential reaction dominating the final picture.

Despite the recent advances in understanding the immunology of delayed hypersensitivity, much work remains to be done. Not only should we try to further elucidate the molecular pathways involved, but we must seek to determine why one cascade is triggered instead of another. In fact, further research is needed in delayed hypersensitivity generally, and in *all* areas of adverse drug reactions, to prevent harm and provide better treatment for our patients.



	Type IV a	Type IV b	Type IV c	Type IV d
Immune reactant	IFN-γ, TNF-α (Th1 cells)	IL-5, IL-4/IL-13 (Th2 cells)	Perforin/ granzymeB Fas ligand (CTL)	CXCL-8 GM-CSF (T-cells)
Antigen	Soluble antigen presented by cells or direct T cell stimulation	Soluble antigen presented by cells or direct T cell stimulation	Cell-associated antigen or direct T cell stimulation	Soluble antigen presented by cells or direct T cell stimulation
Effector mechanism	Macrophage activation	Eosinophils	T cells	Neutrophils
	Chemokines, cytokines, cytotoxins	Cytokines, inflammatory mediators	Apoptosis	Cytokines, inflammatory mediators
Example of hypersensitivity reaction	Tuberculin reaction contact dermatitis (with IVc)	Chronic asthma, chronic allergic rhinitis Maculopapular exanthem with eosinophilia	Contact dermatitis Maculopapular and bullous exanthem Hepatitis	AGEP Behçet disease

T regulatory cells (T-reg: CD4+/CD25+ and/or IL-10/TGF-β secreting cells

Fig. 2. Revised Gell and Coombs classification of delayed drug hypersensitivity reactions. Reproduced with permission by Lippincott Williams and Wilkens: Lerch M, Pichler WJ. The immunological and clinical spectrum of delayed drug-induced exanthems. Curr Opin Allergy Clin Immunol 2004; 4(5):411–419 (2).
IFN = interferon; TNF = tumor necrosis factor; IL = interleukin; CTL = cytotoxic T lymphocyte; GM-CSF = granulocyte-monocyte colony stimulating factor; AGEP = acute generalized exanthematous pustulosis; TGF = transforming growth factor; and CXCL is a chemokine.

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Decrease of Total Antioxidant Capacity during Coronary Artery Bypass Surgery

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Abstract

Objective: Cardiac surgery induces an oxidative stress, which may lead to impairment of cardiac function. In this study, we aimed to measure the changes of oxidative and antioxidative status of patients undergoing coronary artery bypass surgery (CABG).

Materials and Methods: We studied 79 patients who underwent CABG with and without cardiopulmonary bypass (CPB). Of the 79 patients, 39 had CPB and 40 did not. Blood samples were drawn before, during, and after the surgery. Antioxidant status was evaluated by measuring total antioxidant capacity (TAC), and oxidative status was evaluated by measuring total peroxide (TP) levels and oxidative stress index (OSI).

Results: TP and OSI levels increased, while TAC decreased progressively after the beginning of surgery, for all patients. There were negative correlations between TAC levels and aortic cross-clamping period and anastomosis time ($r = -0.553$, $p < 0.001$ and $r = -0.500$, $p < 0.001$, respectively). In addition, there was a positive correlation between TAC and ejection fraction ($r = 0.647$, $p < 0.001$).

Conclusions: During CABG, oxidant and OSI levels significantly increase and TAC significantly decreases. This situation is influenced by long CPB and anastomosis time, and also by low ventricular ejection fraction. We concluded that the patients who undergo CABG are exposed to potent oxidative stress that impairs their TAC. We speculate that supplementation with antioxidant vitamins such as vitamins C and E may be beneficial for patients undergoing CABG.

Key Words: Antioxidant capacity, cardiac surgery, coronary artery bypass grafting, oxidative stress.

Introduction

ISCHEMIA-REPERFUSION INJURY may cause damage to the myocardium following blood flow restoration after a critical period of coronary occlusion (1). In fact, ischemia-reperfusion is a clinical problem associated with procedures such as thrombolysis, angioplasty, and coronary bypass surgery, which are commonly used to reestablish the blood flow and minimize damage to the heart due to severe myocardial ischemia. Two main hypotheses, namely oxidative stress and Ca^{2+}-overload, have been proposed to explain the pathogenesis of ischemia-reperfusion injury (2, 3).

Oxidative stress, which is usually associated with increased formation of reactive oxygen species (ROS), modifies phospholipids and proteins, leading to lipid peroxidation and oxidation of thiol groups (4, 5). These lipids and thiol groups are closely linked to inflammatory responses, including complement activation, release of cytokines, and leukocyte activation, along with expression of adhesion molecules (6). Many studies have described the nature of these ROS and the time course of their formation during cardiopulmonary bypass (CPB) (7). The nature of these oxidative events leads to depletion of plasma antioxidants, increased lipid peroxidation, and formation of other damaging metabolites (1, 8, 9). To learn how to counterbalance this sequence of events and diminish oxidative injury, several studies have investigated the use of antioxidant supplements during extracorporeal circulation (ECC) (10, 11).

Antioxidant molecules prevent and/or inhibit these harmful reactions (12). Serum (or plasma) concentrations of various antioxidants can be measured in laboratories separately, but the measurements are time-consuming, labor-intensive, and costly, and they require complicated techniques. Because measuring different antioxidant molecules separately is not practical, and their antioxidant effects are additive, total antioxidant capacity (TAC) of a sample is measured (13).

In the last few years, off-pump coronary artery bypass surgery (CABG) has gained widespread acceptance as an alternative technique to conven-

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tional on-pump CABG. It has moreover been postulated that off-pump surgery of CPB avoids myocardial ischemia-reperfusion and significantly reduces the postoperative systemic inflammatory response and other biological derangements and, possibly, may improve the clinical outcomes (14). There are only a few studies a comparing the degree of oxidative stress of patients with on-pump vs. patients with off-pump technique, and the results of these studies are debatable (6, 15–17).

In this study, we aimed to measure and compare oxidative and antioxidative status in patients undergoing off-pump and on-pump CABG.

Methods

Patients

Seventy-nine patients elected CABG. Preoperative and postoperative patient data were reviewed using registry databases, medical notes, and charts. Thirty-nine patients (group A) underwent CABG using the CPB technique while 40 patients (group B) were operated on using the off-pump technique. Selection of either technique was made by the individual surgeon, based on his experience and preference.

All patients were on standard anti-anginal treatment, and they all stopped taking aspirin 7 days before the operation. The study was approved by the local ethics committee, and informed consent was obtained from all patients. Patients' data are summarized in Table 1.

TABLE 1
Perioperative and Operative Characteristics of Patients Undergoing Coronary Artery Bypass (CPB) Grafting

Characteristic	Group A (n=39)	Group B (n=40)	p
Age (years)	59.66 ±13.80	63.57±12.72	0.45
Female sex (%)	43.6	37.5	0.58
Current smoker (%)	51.2	67.5	0.14
Diabetes mellitus (%)	17.9	20.0	0.81
Hypertension (%)	38.5	45.0	0.55
Chronic obstructive pulmonary disease (%)	53.8	60.0	0.58
Anastomosis/patient (mean ± SD)	2.03 ± 0.7	1.93 ± 0.7	0.91
Distal anastomosis time (min ± SD)	25.5 ± 4.5	17.5 ± 5.7	0.16
CPB time (min ± SD)	74.3 ± 6.2		
Length of stay in intensive care unit (h ± SD)	15.55±1.58	14.73±1.35	0.46
Length of stay in hospital (d ± SD)	7.33 ± 1.11	7.44 ± 1.14	0.91

Anesthesia and Operative Technique

All routine cardiac medications were continued up to the morning of surgery. After premedication of 5 mg midazolam intramuscularly and 0.18 mg/kg of morphine diluted in 4 mL were given intrathecally for postoperative analgesia, anesthesia was induced using 0.3 mg/kg of etomidate and 1 μg/kg of remifentanil and 0.6 mg/kg of rocuronium intravenously. After endotracheal intubation, desflurane (3–10%) and remifentanil 0.25–1.0 μg/kg/min in air/oxygen and rocuronium were given to maintain the anesthesia.

After the standard median sternotomy, aorta-right atrial cannulation and cardiopulmonary bypass were performed in on-pump patients. During CPB, hematocrit, mean arterial pressure, and pump flow were kept between 20 and 30%, 50–80 mm Hg, and 2.2–2.5 L/m^2, respectively. Adequacy of tissue perfusion was monitored by arterio-venous partial carbon dioxide difference ($P_{v\text{-}a}$ CO_2), urine output, and base deficit. Patients were cooled to 32°C with moderate hypothermia. Desflurane-remifentanil anesthesia was administered during CPB. Revascularization procedures were performed with aortic cross-clamping. During myocardial ischemia antegrade cold hyperkalemic crystalloid cardioplegia was used (Plegisol®, Abbot Laboratories, IL). After completion of distal anastomosis, the proximal anastomosis was performed to the ascending aorta by using a side-biting clamp.

Left internal mammary artery and saphenous vein grafts were harvested for off-pump patients. To provide better access to lateral and posterior target vessels, the pericardium was retracted by two or three deep sutures and two sponges were placed under the heart. Neither a heart stabilizer nor intraluminal shunts were used. Silicone snare sutures were placed proximal and distal to the anastomosis, in order to provide a bloodless field. Remifentanil infusion and desflurane were discontinued at skin closure, and all patients were extubated in the operating room.

Samples

Blood samples were drawn from the central venous catheter immediately before, midway through and at the end of the surgery, as well as 24 h and 48 h after cessation of CABG. The obtained heparinized blood was immediately stored on ice at 4°C. The plasma was then separated from the cells by centrifugation at 3,000 rpm for 10 min, and the plasma samples were stored at –80°C until analysis.

Measurement of TAC

The TAC of the plasma was measured using a novel, automated, colorimetric measurement method developed by Erel (12). In this method, hydroxyl radical, which is the most potent biological radical, is produced. In the assay, ferrous ion solution, which is present in Reagent 1, is mixed with hydrogen peroxide, which is present in Reagent 2. The sequential produced radicals, such as brown-colored dianisidine radical cation, produced by the hydroxyl radical, are also potent radicals. In this assay, the antioxidative effect of the sample against the potent free radicals' reactions, which is initiated by the produced hydroxyl radical, is measured. The assay results are expressed as mmol Trolox equivalent/L; the precision of this assay is excellent. Accurate measurements of TAC can be obtained in as little as 10 min, making this assay eminently suitable for the clinical biochemistry laboratory (18).

Measurement of Total Peroxide Concentration

Total peroxide (TP) concentrations were determined using the FOX2 method with minor modifications (18, 19). The FOX2 test system is based on oxidation of ferrous ion to ferric ion by various types of peroxides contained within the plasma samples, to produce a colored ferric-xylenol orange complex whose absorbency can be measured. The FOX2 reagent was prepared by dissolving ammonium ferrous sulfate (9.8 mg) in 250 mM H_2SO_4 (10 mL), to give a final concentration of 250 μM ferrous ion in acid. This solution was then added to 90 ml of HPLC-grade methanol containing 79.2 mg butylated hydroxytoluene (BHT). Finally, 7.6 mg xylenol orange was added with stirring to make the final working reagent (250 μM ammonium ferrous sulfate, 100 μM xylenol orange, 25 mM H_2SO_4 and 4 mM BHT in 90% vol/vol methanol in a final volume of 100 mL). The blank reagent contained all the components of the solutions except ferrous sulfate. Aliquots (200 μL) of plasma were mixed with 1800 μL FOX2 reagent. After incubation at room temperature for 30 min the vials were centrifuged at 12,000 *g* for 10 min. Absorbency of the supernatant was then determined as a function of the absorbency difference between test and blank tubes, using a solution of H_2O_2 as standard. The coefficient of variation for individual plasma samples was less than 5%.

Oxidative Stress Index

The percent ratio of the TP to the TAC gave the oxidative stress index (OSI), an indicator of the degree of oxidative stress (18–20). To perform the calculation, the result unit of TAC, mmol Trolox equivalent/L, was converted to μmol equivalent/L and the OSI value was calculated by the formula: OSI = [(TP, μmol/L)/(TAC, μmol Trolox equivalent/L)×100].

Statistical Analysis

Results were expressed as mean ± standard deviation. Differences were considered significant at a probability level of $p < 0.05$. Obtained results were evaluated by repeated measurement variance analysis, student's t test correlation analysis, and chi-square tests. SPSS, Systat, and SigmaPlot computer programs were used.

Results

The preoperative characteristics of patients are listed in Table 1. As seen there, no statistically significant demographic differences were observed between the on-pump and off-pump groups. Problems included chronic obstructive airway disease (COPD), hypertension, and diabetes mellitus requiring active treatment at the time of the operation.

The operative characteristics of patients are also presented in Table 1. There was no significant difference in the number of grafts between the off-pump and on-pump patients. CPB patients received 2.03 ± 0.7 grafts per patient, while off-pump patients received 1.93 ± 0.7 grafts per patient ($p = 0.91$). For the CPB patients, distal anastomosis time was 25.5 ± 4.5 min.; for the off-pump patients, 17.5 ± 5.7 ($p = 0.16$).

No patient required exploration for postoperative bleeding, and there were no operative deaths or important adverse complications; all patients were discharged from the intensive care unit on the first postoperative day. There was no significant difference in the length of stay in intensive care unit and length of stay in hospital between the off-pump and on-pump patients ($p= 0.46$; $p= 0.91$).

TAC, TP, and OSI changes are presented in Figs. 1, 2 and 3, respectively. As seen in Fig. 1, in group A (on-pump) patients, TAC decreased during surgery and also for 48 hours postoperatively ($p < 0.005$). OSI level increased progressively after the beginning of surgery ($p< 0.001$). There was a negative correlation between TAC levels and aortic cross-clamping period ($r = -0.553$, $p < 0.001$). There was also a positive correlation between TAC and ejection fraction ($r = 0.647$, $p < 0.001$).

As seen in Fig. 1, in group B (off-pump) patients TAC decreased during the operation and it

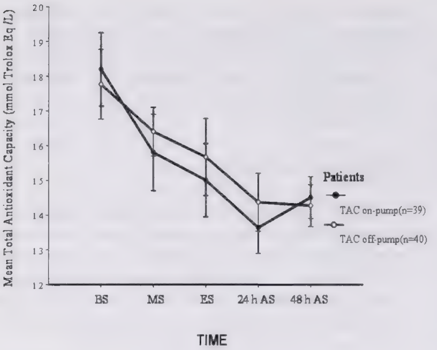

Fig. 1. Time changes of total antioxidant capacity (TAC) during and following on-pump and off-pump coronary artery surgery. All the preoperative, operative, and postoperative values showed statistically significant differences from the baseline value ($p < 0.005$).
BS = before surgery; MS = midpoint of surgery; ES = end of surgery; 24 h AS = 24 hours after surgery; 48 h AS = 48 hours after surgery.

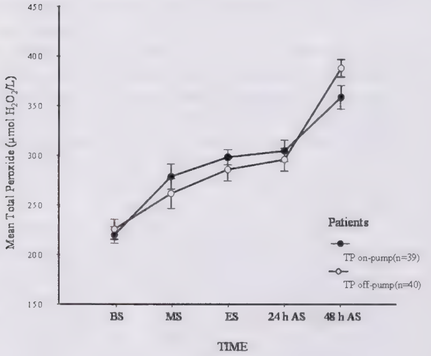

Fig. 2. Time changes of total peroxide (TP) concentration during and following on-pump and off-pump coronary artery surgery. All the preoperative, operative, and postoperative values showed statistically significant differences from the baseline value ($p < 0.005$).
BS = before surgery; MS = midpoint of surgery; ES = end of surgery; 24 h AS = 24 hours after surgery; 48 h AS = 48 hours after surgery.

remained so until 48 hours postoperatively ($p < 0.001$). In addition, as seen in Fig 3, OSI increased progressively on serial blood samples taken from the time of coronary anastomosis ($p < 0.001$). A negative correlation was also obtained between anastomosis time and TAC ($r = -0.500$, $p < 0.001$).

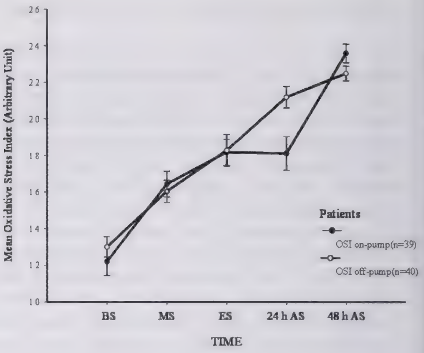

Fig. 3. Time changes of oxidative stress index (OSI) during and following coronary artery surgery for both groups ($p < 0.001$). BS = before surgery; MS = midpoint of surgery; ES = end of surgery; 24 h AS = 24 hours after surgery; 48 h AS = 48 hours after surgery.

TAC, TP and OSI mean and standard deviation (SD) values are presented in Table 2.

Discussion

The systemic increase in oxidative stress during CABG is well-documented (1, 5), but the various components of the oxidant-antioxidant balance and the contribution of the various mechanisms involved have not yet been fully evaluated. This situation is closely connected with overproduction of ROS. ROS is produced during the ischemia/reperfusion process and systemic inflammatory response, both of which are associated with cardiac surgery performed with CPB (6, 15). In the present study, we found that patients undergoing on-pump or off-pump CABG are exposed to potent oxidative stress.

There are only a few studies comparing the degree of oxidative stress for patients undergoing on-pump vs. those undergoing off-pump techniques. However, it has been demonstrated that the on-pump procedure gives rise to a more pronounced systemic inflammation and oxidative stress than the off-pump procedure (14). The mechanisms explaining these observations may be related to several deleterious events occurring during CPB (21), which are either material-dependent (caused by exposure of blood to nonphysiologic surfaces and conditions during the ECC) or material-independent (caused by surgical trauma, ischemia-reperfusion, and changes in body temperature). These events are closely linked to inflammatory responses, including complement activation, release

TABLE 2
TP, TAC, and OSI Mean and Standard Deviation (SD) Values

	BS	MS	ES	24 h	48 h	p
Total Peroxide						
TP on-pump (Mean ± SD)	22.43 ±1.0	26.00 ± 1.5	28.40 ± 1.2	29.40 ± 1.1	38.54 ± 0.9	0.001
TP off-pump (Mean ± SD)	21.86 ± 0.8	27.70 ± 1.3	29.63 ± 0.8	30.26 ± 1.1	35.63 ± 1.2	0.001
Total Antioxidant Capacity						
TP on-pump (Mean ± SD)	1.82 ± 0.10	1.58 ± 0.11	1.50 ± 0.10	1.36 ± 0.07	1.45 ± 0.06	0.001
TP off-pump (Mean ± SD)	1.78 ± 0.10	1.64 ± 0.07	1.56 ± 0.11	1.44 ± 0.08	1.43 ± 0.60	0.001
Oxidative Stress Index						
TP on-pump (Mean ± SD)	1.22 ± 0.08	1.66 ± 0.07	1.82 ± 0.07	1.81 ± 0.09	2.36 ± 0.05	0.001
TP off-pump (Mean ± SD)	1.30 ± 0.05	1.62 ± 0.06	1.82 ± 0.09	2.12 ± 0.06	2.25 ± 0.04	0.001

BS = before surgery; MS = midpoint of surgery; ES = end of surgery.

of cytokines, and leukocyte activation, along with expression of adhesion molecules (6). Many studies have described the nature of these ROS and the time course of their formation during CPB (7). These oxidative events in turn lead to depletion of plasma antioxidants, increased lipid peroxidation, and formation of other damaging metabolites (1–11). In our present study, we demonstrated that off-pump patients experience decreased oxidative stress compared with patients undergoing CPB, but this difference is not significant statistically (Fig. 1–3 and Table 2).

Oxidative stress is the result of imbalance between antioxidant defenses and the formation of ROS. Oxygen-free radicals and their metabolites play an important role in the pathophysiology of ischemia-reperfusion injury. However, direct measurement of free radicals in humans is difficult because of the free radicals' transient nature and the complexity of the available techniques. Various measurement methods have been developed for total antioxidant status, but there is as yet no accepted reference method (12, 13). The most widely used methods for TAC measurement utilize colorimetry, fluorescence, and chemiluminescence (22–24). In these methods, a type of radical is generated in the assay and the antioxidant activity of the sample is measured against that of the assay radical. On the other hand, even when these technologies are available, their value is limited. In the present study, the total antioxidant status of the plasma was measured using a novel automated colorimetric measurement method developed by Erel for patients undergoing off-pump and on-pump CABG (12).

Reintroduction of oxygen to previously hypoxic myocardium can result in a sudden increase in the extent of irreversible tissue injury. There is abundant evidence that the mechanism of ischemic-reperfusion injury involves increased generation of ROS, and that both endogenous and exogenous antioxidants and antioxidative enzymes ameliorate the extent of the damage (25–30). The recognition of these pathogenic mechanisms has made the understanding of the natural antioxidant defenses, intracellular and extracellular, of clinical importance.

Several studies have shown a direct connection between increased production of ROS and damage of tissues and organs, as well as deleterious effect of these substances on heart function (6, 14–17). In the present study, TAC decreased during surgery and for 48 hours postoperatively ($p < 0.005$), while the total peroxide increased ($p < 0.001$) operatively and postoperatively in all patients. However, this difference is not statistically significant between the groups.

Depending on the severity of the ischemic period, oxidative stress occurs during the reperfusion of patients with coronary artery disease who are subjected to on-pump cardiac surgery, and that stress may be linked to a delay in postoperative recovery of cardiac function. As previously proposed, not only is chronic ischemia responsible for a severe impairment of myocardial contractility, but it can also promote a loss of tissue glutathione and scavenging enzyme activity (by glutathione peroxide), thus resulting in a lack of defense against free radical toxicity (27). Prolonged ischemia is responsible for a decrease in myocardial non-protein sulphydryl groups, mainly glutathione and high-energy phosphates, and this becomes a rate-limiting factor for detoxification of oxygen species (31). The final effect could be a vicious circle in which chronic ischemia impairs left ventricular ejection fraction and reduces natural scavenger availability, thus producing a low ability to counterbalance the damage of ischemia and worsening myocardial contractility (15). Patients with low left ventricular ejection fraction did not have lower preoperative TAC values or higher lipid peroxidation following CABG. However, they exhibited a more prominent plasma antioxidant depression immediately after surgery. This might be due to exacerbation of albumin loss into the extracellular space and through the kidneys, as well as decreased levels of vitamin C, observed in chronic heart failure (15). We found a positive correlation between TAC and ejection fraction ($r = 0.647$, $p < 0.001$). To the best of our knowledge, this is the first report showing the relationship between the TAC and ejection fraction.

We also found that there was a significant inverse correlation between TAC and cross-clamp time ($r = -0.553$, $p < 0.001$). To the best of our knowledge, this is the first report showing the inverse relationship between the TAC and cross-clamp time in the patients. Ferrari and coworkers, using a crystalloid cardioplegia, reported a positive correlation between cross-clamp time and oxidized glutathione release for clamping periods longer than 30 minutes, while the correlation was not evident for periods less than 30 minutes (27). On the other hand, we found positive correlations between cross clamp-time and TP and OSI.

In conclusion, during CABG, oxidants and OSI levels increase significantly and TAC decreases significantly. This situation is influenced by long CPB/anastomosis time and low ventricular ejection fraction. We conclude that patients who are undergoing CABG are exposed to potent oxidative stress and that their TAC is impaired. Therefore, prior to coronary bypass surgery, we suggest that supplementation with antioxidant vitamins such as vitamin C and E may be beneficial.

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Surgery for Hyperthyroidism in Down Syndrome:

Case Report

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Abstract

Thyroid disorders are common in patients with Down syndrome (DS). In these patients, hyperthyroidism occurs much less frequently than hypothyroidism, but it is likely to be underestimated. We report a case of an adult man with DS and hyperthyroidism. Ater 2 years of antithyroid therapy in a special facility, he was referred to our center with recurrence of hyperthyroidism with leukopenia and elevations of liver enzymes 14 months after remission. The patient underwent subtotal thyroidectomy, with rapid preparation with inorganic iodine and prednisone. After thyroidectomy the patient was found to have hypothyroidism and was given thyroid replacement therapy. We also review the literature on the treatment options for hyperthyroidism with DS. We conclude that the role of surgery in the treatment of hyperthyroid patients with DS has yet to be defined.

Key Words: Hyperthyroidism, Down syndrome, surgery.

Introduction

THYROID DISORDERS occur with increased frequency in patients with Down syndrome (DS). The overall incidence of thyroid dysfunction ranges from 7% (1) to more than 50% (2), depending on the sample size, the selected population, and the criteria for diagnosis. The etiology of most acquired thyroid disorders in DS is believed to be an autoimmune disturbance.

Hyperthyroidism occurs much less frequently than does hypothyroidism among individuals with DS (3). A community-based study of 138 individuals with DS found 28 to be hypothyroid and 2 to be hyperthyroid (4). Hyperthyroidism associated with DS usually occurs as a result of diffuse enlargement of the thyroid gland (Graves' disease).

All guidelines recommend yearly screening for thyroid disease, since the frequency increases with age and is reported to be greater than 15% in individuals with DS (5).

Graves' disease definitely requires treatment. Treatment options for hyperthyroidism are surgery, medical treatment, and radioactive iodine therapy.

Case Report

The patient was a 43-year-old Turkish man. Developmental retardation had been noted at the age of 6 months, and the diagnosis of DS was made. Chromosomal analysis revealed a regular trisomy-21-karyotype (47,XY,+21). He has been followed by personnel at a special rehabilitation center since the age of 13 years.

The case history begins in November 2001, when a physician in a specialized medical facility noted that the patient had a diffuse vascular goiter. Physical examination revealed sinus tachycardia, excessive sweating, and warm hands with fine tremors, but there was no evidence of Graves' ophthalmopathy. Thyroid studies were consistent with hyperthyroidism. A thyroid scan showed enlargement of both lobes. There were no available data for TSH receptor antibody and thyroid ^{131}I uptake. Antithyroglobulin antibody was increased; antithyroid peroxidase antibody was normal. The physician started antithyroid medication and followed the patient with tests for periodic liver enzymes and whole blood count. In March 2003, re-

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mission was achieved. In May 2003, recurrence of hyperthyroidism was diagnosed, and after a short time during which there was an elevation of liver enzymes and leukopenia was diagnosed, Propycil® (propylthiouracil) was started again. (This is not advisable, since further exposure to the drug may cause hepatitis and further decrease of the low neutrophil count.) The patient also had a history of diabetes mellitus, which for 5 years had been controlled by diet and oral antidiabetics.

The patient was referred to our clinic in November 2003. He had a fever (38.3°C) and his thyroid gland was large, diffuse, and palpable. Splenomegaly and corneal opacities were observed during physical examination. His blood pressure was 110/70 mm Hg, and his pulse rate was 76 beats per minute. His weight was 86 kg and his height was 179 cm. Sedimentation rate and C-reactive protein were within the normal range. Results of thyroid function tests were total T_4: 29.2 μg/dL; total T_3: 5.3 ng/mL; and sTSH: 0.01 IU/mL.

Laboratory analyses revealed the following levels: alanine aminotranferase, 112 U/L; aspartate aminotransferase, 64 U/L; glutamyl transpeptidase, 67 U/L; alkaline phosphatase, 310 U/L; white blood cell count, 2,000/mm^3 (normal: 4,500–11,000/mm^3); neutrophil count, 1,200/mm^3 (2,000–7,800/mm^3); thrombocyte count, 41,000/mm^3 (150, 000–400, 000/mm^3); zinc, 81 μg/dL (range, 70–150 μg/dL); folic acid, 11.3 ng /mL (range, 3–17 ng /mL); and vitamin B12, 199 pg/mL (157–1059 pg/mL). (Patient was on vitamin B12 replacement therapy.) In addition, his hepatitis B antigen was positive. Patient's low neutrophil and thrombocyte count may have been related to his liver disease, antithyroid drug therapy, and thyrotoxic status.

A thyroid ultrasound revealed no nodularity. Blood and urinary cultures were negative. The thyroid ^{131}I uptake was 19.9% (normal: 6–18 %) after 4 hours and 67% (normal: 10–30%) after 24 hours. TSH receptor antibody, antithyroid peroxidase, and antithyroglobulin levels were within normal limits.

A bone marrow biopsy revealed normocellular bone marrow, a liver biopsy revealed chronic hepatitis B (precirrhotic liver), and an endoscopic biopsy revealed chronic atrophic gastritis. Tests for anti-islet and anti-GAD antibodies were negative.

Due to the late effect of radioactive iodine (RAI) therapy, we did not consider this modality as a first-line measure. The patient was prepared for surgery in 10 days, with a regimen of prednisone (30 mg/day) and inorganic iodine (3 times a day) (6). In addition, propranolol was given in a dose of 120 mg daily to relieve associated symptoms such as palpitation. Because of the patient's severe degree of mental retardation (IQ 35), his brother signed the consent form for the treatment. The patient underwent a subtotal thyroidectomy 1 week later, with no adverse events. A diffuse enlarged gland and hyperplasia were found on histopathology.

When thyroid function was assessed 1 month postoperatively, a profile of definite hypothyroidism was noted. It was decided that the patient needed thyroid replacement therapy with L-thyroxine, and this was started. The dose of L-thyroxine was then adjusted according to the thyroid function, until a replacement daily level was reached. Thyroid function was checked every 6 months thereafter, and the patient continued to require thyroxine replacement (100μg/day). The patient's liver enzymes and white blood cell count have returned to normal values during follow-up (after 2 months).

Discussion

Hyperthyroidism in patients with DS is an uncommon condition (1, 3–5). The symptoms of hyperthyroidism may be missed in patients with mental retardation. Because of this, routine thyroid function testing must be done for patients with DS.

Once the diagnosis of Graves' disease has been made, an appropriate treatment modality must be selected, depending on the presence of associated medical conditions.

There is a lack of consensus on the role of thyroidectomy in the treatment of Graves' disease. Surgical intervention involves partial thyroidectomy, but this is rarely undertaken in patients with DS. Also, no real data are available about thyroid surgery for patients with DS and Graves' disease. Aberrant craniofacial features frequently seen in individuals with DS include short neck, prominent (macroglossia) furrowed tongue, midfacial and mild mandibular hypoplasia, and general muscle hypotonia (7). These craniofacial anomalies of patients with DS lead to a higher incidence of obstructive airway problems, such as difficulties during anesthetic induction and emergence. The three most frequent anesthesia-related complications among patients with DS are bradycardia, natural airway obstruction, and postintubation stridor (7). Also, these patients, because of their short necks, may present a surgical risk for thyroidectomy. A smaller diameter endotracheal tube for intubation was used in our patient.

For our patient, surgery was the therapy of choice for recurrence of hyperthyroidism, because of concomitant leukopenia and liver enzyme elevation. It is not advisable to give Propycil again after leukopenia and liver enzyme elevation. RAI was not a choice because of the late effect of this therapy modality. Successful surgery tends to terminate the thyrotoxic state within a few days, and the prompt effect of surgery may indeed be particularly desirable for these patients (8).

Hyperthyroidism in DS is generally treated with carbimazole, propylthiouracil or radioactive iodine (9, 10). Most of the cases in the litarature treated with RAI achieved remission (11,12). However, there may be contraindications for the use of antithyroid medication. For patients in whom its use is contraindicated, surgery with rapid preparation may be considered. The practice of surgery for hyperthyroid children with DS is debatable.

Conclusions

Hyperthyroidism is an uncommon condition in patients with DS, but one that is likely to be underdiagnosed and underreported. There is no consensus in the DS literature on the role of surgery. However, for some patients with hyperthyroidism and DS, surgery may be the preferred treatment modality.

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A Cost-Effective Method for Reducing the Volume of Laboratory Tests in a University-Associated Teaching Hospital

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Abstract

BACKGROUND: Laboratory tests comprise a significant portion of hospital expenditure. Attempts to reduce their use have had mixed results.

OBJECTIVE: To investigate the effect of an intervention based on a simple form-based system for ordering laboratory tests by physicians, on both use of laboratory resources and diagnostic accuracy.

DESIGN: At Kaplan Medical Center in Rehovot, Israel, there are 4 similar internal medicine departments. In one department (C), the new system was initiated, whereas in the other 3 departments (A, B and D), the traditional method of ordering blood tests was continued. The intervention used was a requirement for tests to be specifically requested by residents following unbundling of test panels, with hands-on supervision by a senior physician. In addition, the residents attended a series of lectures on the economic implications of laboratory testing. The intervention study lasted for 3 years.

MEASUREMENTS: Total number of tests performed in each department, number of tests per admission and total cost of each test at Medicare reimbursement prices.

RESULTS: The number of tests per admission prior to the intervention was 1.91± 0.89; it decreased for each of the next 3 years: 0.76±0.61, 0.80±0.62 and 0.78±0.63 respectively. There was a total decrease of 97,365 tests during the 3-year period, saving $1,914,149. There was no difference in the readmission rate or in the number of diagnoses of conditions based primarily on blood tests such as hypokalemia or hyponatremia, between department C and the other departments.

CONCLUSIONS: The intervention developed here produced significant and sustained reduction of financial savings in the number of laboratory tests ordered, without negatively impacting diagnostic capability or patient care.

Key Words: Cost reduction, laboratory, testing, hospital.

Introduction

DURING THE LAST SEVERAL DECADES there has been an increase in the use of laboratory tests by physicians. These tests are considered essential tools for disease screening, diagnosis and monitoring. Although laboratory testing represents an enormous expenditure (1), there is wide variation in its use for similar indications (2–4), and some diagnostic testing is probably inappropriate (5), although the evidence to support this is weak (6).

Several explanations have been offered to explain the variation in the use of diagnostic tests, including the inability of physicians to predict test performance characteristics, inaccurate interpretation of diagnostic test results, and difficulties in mastering the most effective diagnostic strategies (7–14). In addition, tests may be ordered for defensive reasons (15), ease of access (16), fear of uncertainty (17), or "test addiction" (18–20). With increasing economic pressures worldwide on health systems, attempts are being made to achieve a more cost-effective use of laboratory resources.

Six general methods of reducing the number of unnecessary tests by changing physicians' practices have been described: education, feedback, physician participation in efforts to produce change, administrative rules, financial incentives and penalties (21). A systematic Medline review of 102 articles reporting the results of interventions aimed at changing physicians' testing practices (19) found that the majority of interventions reported claimed some success, but that those interventions based on multiple behavioral factors were most successful. However, many approaches have been criticized as being time-consuming (22), difficult to implement institutionally (23), counter-

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productive to physician training (24), detrimental to clinical decision making (25), or too intrusive (26).

More recently, the use of information systems to improve health care delivery has been suggested (27), especially in the area of care provider order entry (CPOE) (28). A recent study from Vanderbilt University has reported the sustained success of an intervention based on software for the CPOE system (29). This technique requires an initial investment of resources and may not be appropriate for poorer countries. In addition, it may not be easily applicable in every institution, or in different systems in different countries.

We have developed a multi-faceted intervention, not based on software changes, in order to reduce the expenditures for lab tests, in an internal medicine department of a university-associated medical center. The purpose of this study was to investigate if any savings in the cost of lab testing could be achieved over a several-year period without compromising the quality of medical care.

Methods

Background

Kaplan Medical Center is a 650-bed university-affiliated hospital in Rehovot, Israel. It serves a population of 350,000 and there are approximately 16,000 medical admissions per year. There are 4 internal medicine departments that admit patients, each on an equal basis. Each department receives every fourth patient requiring admission. Medical manpower is nearly identical in each department, with a total of 11 physicians on staff. The internal medicine departments are responsible for 25% of all laboratory investigations in the medical center, compared to 8.4% for the surgery departments. The vast majority (>98%) of admissions to the internal medicine departments are via the department of emergency medicine.

In the emergency department, initial blood tests are performed. These include a complete blood count (CBC), coagulation profile, blood urea nitrogen (BUN), serum sodium, potassium, and glucose for all admitted patients. Additional tests, as for bilirubin, amylase creatine phosphokinase (CPK), troponin and arterial blood gases, are performed at the discretion of the admitting physician in the emergency room.

In the department of internal medicine, a first-day profile of blood tests is taken. This includes: erythrocyte sedimentation rate (ESR), CBC, glucose, urea, sodium, potassium, calcium, phosphorus, BUN, creatinine, uric acid, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, and a coagulation profile. In addition a lipid profile, CPK, CPK of muscle band (CPK-MB), serum troponin and amylase may be ordered at the discretion of the admitting physician in the department (one of the department residents). The form and the test tubes for the blood tests are prepared by nursing students at night on the basis of a set of instructions written in a notebook by the residents during the evening rounds. These tests include not only the first-day profile, but also additional tests ordered by the residents as they see necessary.

We decided to initiate a multi-tiered program in order to reduce the use of lab tests on a continuous, sustainable basis without impacting negatively on patient care. In order to do so, we chose the following approach:

1. We organized a lecture to the residents and senior physicians of Department of Internal Medicine C, describing the economic implications of the excessive use of blood tests and drawing attention to the current inappropriate ordering of blood tests (e.g., testing the lipid profile 3 times during a 3-day admission for unstable angina).
2. We included the residents in the process of changing the current method of ordering blood tests.
3. We made an administrative change. The required blood test needed to be specifically ordered by the resident, instead of ordering large groups of tests (e.g., lipid profile, SMA analysis). This meant the unbundling of serum metabolic panel tests. The other three departments of internal medicine were informed of the unbundling of the serum metabolic panel tests and received a short lecture from one of the physicians from Department C (MA) regarding the expenditure incurred due to lab tests.
4. A senior physician of the department supervised the ordering of the lab tests. This step would also be included, with the chance for hands-on teaching regarding the problems of the patient and the pertinence of the relevant blood tests.

An estimate of cost was obtained by computing the hospital fees that Medicare reimburses for routine blood tests (data supplied from the billing department, Newton-Wellesley Hospital, Newton, MA). We chose to use the costing system common in the U.S. so that any total savings would be more relevant to an audience outside of Israel.

For statistical analysis, we used the SPSS program (11th edition). Student's t-test was performed and was 2-tailed. A p value of less than 0.05 was regarded as significant. The study of this program lasted for 3 years.

Results

In order to assess the impact of the program of intervention, it was first necessary to determine the number of lab tests performed in Internal Medicine C in the period before the intervention was initiated. For the period from July 1, 2000 to June 30, 2001, there were a total of 15,073 days of hospital admission and 4,158 admissions. The numbers of routine biological tests are shown in Table 1. The range was from 20 for glycosylated hemoglobin (HbA_{1c}) to 9,291 for serum glucose determinations. The average number of investigations per hospital admission for each parameter was calculated and is also shown in Table 1. There was no significant difference in the mean number of tests performed per admission between the 4 internal medicine departments prior to the intervention (Fig. 1).

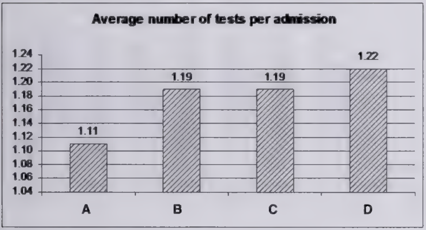


Fig. 1. The mean number of tests per admission prior to starting the intervention.
$p > 0.5$ for comparison between Department C and the other departments.

TABLE 1
Number of Tests Ordered and Number per Admission for the Department of Internal Medicine C from July 1, 2000 to June 30, 2001, prior to the Start of the Intervention

Test	Number Ordered	Number per Admission
Amylase	3640	0.88
Antinuclear Ab	200	0.05
Cholesterol, HDL	762	0.18
C-Reactive Protein	619	0.15
D-Dimer	172	0.04
Ferritin	373	0.09
Folic Acid	281	0.07
GGT	1867	0.45
Hemoglobin A1C %	20	0
HGB	8188	1.97
Iron	483	0.12
Myoglobin , Blood	101	0.02
PT %	5947	1.43
PT-INR	5947	1.43
Transferrin	441	0.11
TSH	964	0.23
Vitamin B12	566	0.14
Cholesterol, LDL	792	0.19
Creatinine	8840	2.13
Glucose	9291	2.24
Potassium	9155	2.20
Sodium	9155	2.20
Urea	9137	2.20
Albumin	7824	1.88
Alk. Phosphatase	7806	1.88
Bilirubin, Direct	8007	1.93
Bilirubin, Total	8007	1.93
Calcium	7950	1.91
Cholesterol	7392	1.78
CPK	7536	1.81
GOT (AST)	7864	1.89
GPT (ALT)	7859	1.89
LDH	7996	1.92
Phosphorus	7786	1.87
Protein, Total	8040	1.93
Triglycerides	7374	1.77

PT = prothrombin time, PT-INR = PT/international normalized ratio, GGT = gamma-glutamyl transferase, HGB = hemoglobin, TSH = thyroid-stimulating hormone, CPK = creatine phosphokinase, LDL = low-density lipoprotein, HDL = high=density lipoprotein, GOT(AST) = glutamic-oxaloacetic transaminase (aspartate aminotransferase), GPT(ALT) = glutamic pyruvic transaminase (alanine transaminase).

Following the initiation of the new program for ordering blood tests, there was a significant decrease in the number of tests per hospital admission for all the major laboratory tests ordered from the Internal Medicine C Department (Fig. 2). Prior to the intervention the mean number of blood tests per admission was 1.19±0.89, and the values for the subsequent 3 years (the intervention period) were 0.76±0.61, 0.80±0.62 and 0.78±0.63, respectively ($p < 0.05$ for all tests). This decrease in the number of tests ordered per admission was maintained during the course of the next 2 years, during which the new method of ordering blood tests was continued.

No change in the work methods of the other internal medicine departments was carried out. Fig. 3 shows the mean number of laboratory tests per admission for each of the other internal medicine departments for the year prior to the study and the 3 years of the study. The pattern of test usage for each department was similar during the period of the study. Interestingly, in all departments, following the initial intervention in Department C, there was a decrease in the mean number of blood tests ordered per admission, then a subsequent rise, followed by another decrease, during the 3-year pe-

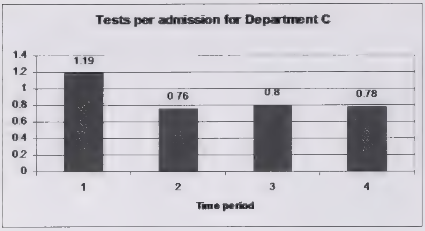


Fig. 2. The number of tests per admission for the Department of Internal Medicine C.
Period 1 = July 1, 2000– June 30, 2001 (prior to the intervention). Period 2 = July 1, 2001–June 30, 2002. Period 3 = July 1, 2002– June 30, 2003. Period 4 = July 1, 2003–December 31, 2004.

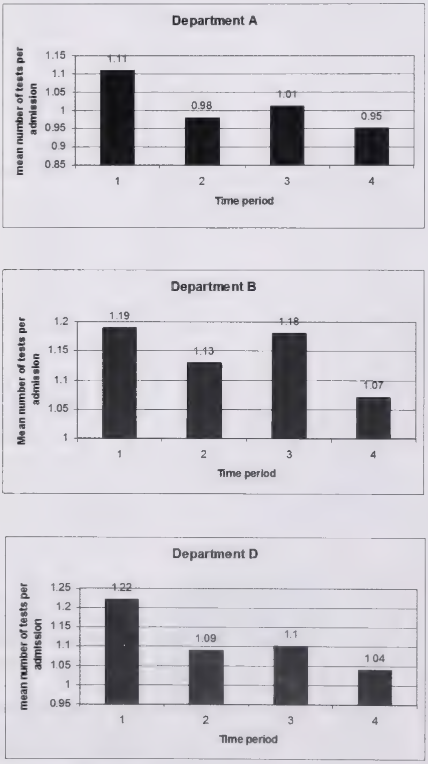
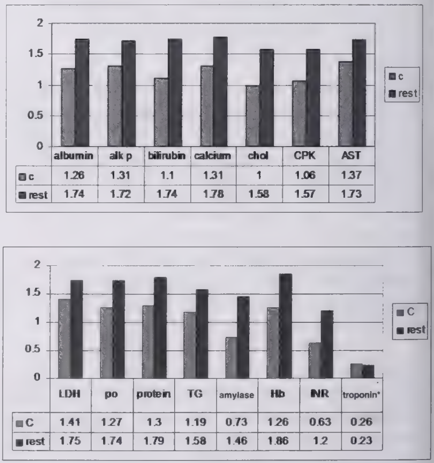


Fig. 3. The mean number of tests per admission for departments A, B and D for each of the time periods described in Fig. 2.

riod. We suggest that this reflects a "spillover" of the intervention to the other departments based on verbal reports from the hospital administration, followed by a lack of reinforcement, and then subsequently another decrease following reinforcing comments from the hospital administration.

In Fig. 4 the mean number of tests per admission for several of the most common tests is shown for the Department of Internal Medicine C versus a mean of the other 3 departments combined. It shows a significantly lower usage of each of these tests by the Department of Internal Medicine C compared to the other departments, for all tests except for troponin. During this period of time, the test for troponin was introduced into the diagnostic armamentarium at Kaplan Medical Center, together with a clear protocol for its use, and each department received an explanatory lecture from the cardiologists prior to starting the test. The usage of this test was similar in all 4 departments. This suggests that physician behavior is an ac-



	albumin	alk p	bilirubin	calcium	chol	CPK	AST
▨ c	1.26	1.31	1.1	1.31	1	1.06	1.37
■ rest	1.74	1.72	1.74	1.78	1.58	1.57	1.73

	LDH	po	protein	TG	amylase	Hb	INR	troponin*
▨ C	1.41	1.27	1.3	1.19	0.73	1.26	0.63	0.26
■ rest	1.75	1.74	1.79	1.58	1.46	1.86	1.2	0.23

Fig. 4. A comparison between the Department of Internal Medicine C and the other 3 internal medicine departments grouped together for a series of laboratory tests per admission. The figures refer to the mean number of tests per admission after the intervention (±95% confidence intervals.
alk P = alkaline phosphate; chol = cholesterol; CPK = creatine phosphokinase; AST = aspartate transaminase; LDH = lactate dehydrogenase; po =phosphorus; TG = triglycerides; Hb = hemoglobin; INR = international normalized ratio.
C refers to the Department of Internal Medicine C and the other group represents the three other departments grouped together. All of the differences had a p value < 0.05, except for troponin.
* p = 0.4.

TABLE 2

Total Number of Admissions for Each of the Internal Medicine Departments for the Years 2000 to 2004. There Was No Significant Difference between the Departments for the Years 2002 to 2004. Prior to this, the Department of Internal Medicine D Was Only Operating on a Reduced Schedule, and thus the Numbers Are Smaller

Year	A	B	C	D
2000	4,535	4,452	4,513	2,634
2001	3,854	3,882	3,910	3,758
2002	3,879	3,906	3,911	3,815
2003	3,945	3,942	3,910	3,618
2004	3,293	3,311	3,383	2,922

quired characteristic and that appropriate conditioning and education of physicians when a new test is introduced can result in a more rational use.

The admissions to the 4 internal medicine departments are completely random, and thus there is likely to be a high degree of homogeneity for the hospitalized patients between departments. It is likely that the medical treatment is similar in all 4 departments, although we do not have any data to confirm or refute this assumption. The total number of admissions was very similar in departments A, B and C throughout the 3 years following the intervention (Table 2). Department D, which was a new department, operated at a lower than full capacity for the years 2000 and 2001 and thus had a smaller number of total admissions during this period. It subsequently operated at full capacity and had a similar number of admissions.

We estimate that our intervention resulted in a saving of 97,365 laboratory tests in the three-year period. There was a total of 1,017,401 tests performed in departments A, B and D during this 3-year period, which is an average of 339,113 tests per department during the 3-year period. The actual number of test performed by Department C during this period was 241,768. Thus the difference is 97,345 tests.

TABLE 3

Number of Tests per Admission for the Period prior to Intervention, for the Departments of Internal Medicine

Test	C	A	B	D
Albumin	1.88	1.61	1.86	1.95
Alk. Phosphatase	1.88	1.60	1.84	1.94
Bilirubin, Direct	1.93	1.67	1.92	2.04
Bilirubin, Total	1.93	1.67	1.92	2.04
Calcium	1.91	1.63	1.89	2.00
Cholesterol	1.78	1.46	1.61	1.85
CPK	1.81	1.57	1.80	1.85
GOT (AST)	1.89	1.62	1.85	1.96
GPT (ALT)	1.89	1.62	1.85	1.96
LDH	1.92	1.64	1.88	1.98
Phosphorus	1.87	1.60	1.85	1.94
Protein, Total	1.93	1.65	1.89	2.02
Triglycerides	1.77	1.46	1.60	1.85
Amylase	0.88	1.55	1.71	1.0
Antinuclear Ab	0.05	0.05	0.1	0.04
Cholesterol, HDL	0.18	0.6	0.13	0.13
C-Reactive Protein	0.15	0.07	0.14	0.08
D-Dimer	0.04	0.04	0.07	0.06
Ferritin	0.09	0.04	0.07	0.06
Folic Acid	0.07	0.07	0.07	0.05
GGT	0.45	0.86	0.87	0.53
Hemoglobin A1C %	0	0.02	0.01	0.01
HGB	1.97	1.77	1.9	2.19
Iron	0.12	0.08	0.09	0.07
Myoglobin, Blood	0.02	0.04	0.03	0.05
PT %	1.43	1.63	1.36	1.06
PT-INR	1.43	1.63	1.36	1.06
Transferrin	0.11	0.07	0.06	0.06
TSH	0.23	0.2	0.21	0.21
Vitamin B12	0.14	0.15	0.12	0.08

$p > 0.3$ for all the other departments compared to C.
See Table 1 for definitions of abbreviations.

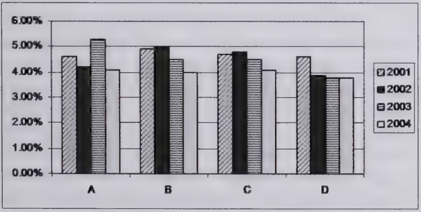


Fig. 5. Readmission rate for each department per time period. $p > 0.5$ between Department C and the other departments for each time period.

In order to determine whether the decreased number of lab tests ordered as a result of this intervention impacted on diagnostic accuracy, we examined the incidence of conditions that are diagnosed mainly on the basis of lab tests, e.g., hyponatremia, hypercalcemia and anemia. We determined the total number of patients with hyperkalemia, hypokalemia, hypernatremia, hyponatremia, hypercalcemia and anemia that were diagnosed in the lab for each department for each time period. The definitions of hyper- or hypokalemia, hyper- or hyponatremia and hypecralcemia were based on a result above or below the normal limits for the Kaplan Medical Center laboratory.

There was no significant difference in the number of cases diagnosed with anemia, hyponatremia, hyperkalemia or hypercalcemia between Internal Medicine C and the other three internal medicine departments following the CPOE inter-

TABLE 4

Mean Number of Diagnoses per Year of Hyponatremia, Hyperkalemia, Hypokalemia, Hypercalcemia and Anemia in Department C Compared to the Average of the Other Three Departments

Diagnosis	Department C	Other 3 Departments
Hyponatremia	55.33	55
Hyperkalemia	10	17.23
Hypokalemia*	30	18
Hypercalcemia	20.33	15.53
Anemia	238.3	234.61

* $p<0.05$

vention. There was, however, a significant increase in the number of cases of hypokalemia diagnosed (Table 4). This suggests that the decrease in the number of tests ordered did not result in a decreased diagnostic ability for conditions that are laboratory-dependent for diagnosis.

In order to determine whether the intervention affected the quality of care, we looked at the rate of readmission within 2 weeks following the initial discharge. The internal medicine departments in Israel have a very aggressive policy on discharge, with a high rate of bed turnover and a short length of stay. This is in part necessitated by a low number of hospital beds. There was a steady decrease in the rate of 2-week readmission for all of the departments during the period of the study. There was, however, no statistically significant difference in the 2-week readmission rate between department C and the other departments (Table 5). Taken together, the similarity between the departments in terms of both diagnostic numbers for laboratory-dependent diagnoses and readmission rates, suggests that the change in policy of ordering lab tests did not negatively impact on patient care.

In order to estimate the savings achieved by this intervention, we calculated the total cost of the tests performed on the basis of the charges that would have been submitted to Medicare. During the 3-year period of the intervention, a total of 348,737 laboratory tests were performed, which would have been billed for a total of $2,318,828. The other three departments performed a total of 1,741,864 tests, at a total cost of $12,698,130. The average cost per department was thus $4,232,977 over the 3-year period. The difference in cost between this average and the cost of the tests performed by department C is $1,914,149. This represents a saving of $638,049 per department per year.

TABLE 5

Readmission Rates during the Two Weeks Following Discharge in the Departments of Internal Medicine from 2001 through 2004

Year	Dept A	Dept B	Dept C	Dept D
2001	4.6%	4.9%	4.7%	4.6%
2002	4.2%	5%	4.8%	3.9%
2003	5.3%	4.5%	4.5%	3.8%
2004	4.1%	4%	4.1%	3.8%

The cost of the intervention is difficult to assess but is likely to be very small. The initial lecture to the medical staff lasted one hour and replaced a formal continuing medical education (CME) session in the department. The interaction with a senior physician took place together with the usual supervision of residents on the afternoon rounds. Thus no extra salary costs were incurred. In addition, there was a 3.5% increase in total admission days from 2001 to 2004 (from 13,815 to 14,294 days) and a 4.6% increase in the number of admissions (from 3,910 to 4,906). Thus, despite the interventions described above, the same medical staff treated more patients, with a resulting increase in the income generated by the department.

Discussion

We have developed a CPOE system that achieved a marked, sustainable decrease in the test-ordering behavior of residents in an internal medicine department of a university-affiliated teaching hospital. The intervention chosen does not require sophisticated software development.

It is widely acknowledged that there is a need for a rational, cost-effective approach to the ordering of laboratory tests. The U.S. Institute of Medicine has recommended the use of information systems to improve health care delivery (27). It has been shown that computer-based reminders (19, 30–32) and "just-in-time" decision making can improve test-ordering practices (33). CPOE systems have been employed previously (28, 29). They have been shown to be an effective method of changing ordering procedures (32, 34) that result in reduced variability in provider behavior (35).

We describe a CPOE method of ordering lab tests that is easy to establish, requires no sophisticated equipment or investment of resources, and produces clear and sustained results. After the initial lecture to the resident staff and the regular presence of a senior physician to discuss with the residents the ordering of blood tests, there was a marked and consistent decrease in the number of blood tests ordered. In the Kaplan Medical Center, the admissions to the four internal medicine departments are randomly allocated. Each department receives every fourth admission. Since they have an equivalent allocation of both material and human resources and similar numbers and types of patients, the other departments can act as a control. The differences between the other internal medicine departments and our department were significant and maintained over the course of three years.

During this period the test for serum troponin was introduced together with clear guidelines to physicians. Interestingly, the use of troponin was similar for all the departments. This suggests that conditioning of physician behavior is possible and is easily achieved if a new test is introduced together with clear guidelines. It is, however, much harder to change physician behavior with well-established tests.

There is a possibility that the decrease in the use of lab tests could negatively impact diagnosis or treatment. We examined the incidence of conditions that are diagnosed mainly on the basis of lab tests in modern medicine—e.g., disturbances in sodium, potassium, calcium or magnesium levels, as well as anemia. We found no significant differences in the incidence of these diagnoses between the different departments. Thus, we believe it is unlikely that our diagnostic ability was impaired as a result of the lower rate of utilization of lab tests in Department C.

In order to check for any adverse effect on the quality of patient care, we determined the readmission rate (within 2 weeks) for each of the internal medicine departments. There was no significant difference in the readmission rates between the 4 departments of medicine, although interestingly there was a steady decline in the readmission rate in each department over the 3-year period of the study. Thus the decrease in the number of blood tests ordered did not result in a decrease in the number of diagnoses that are based mainly on lab test results, nor on the quality of care as represented by the rate of readmissions within 2 weeks of discharge.

Excessive laboratory testing is likely to generate a number of false positive blood tests or incidental findings of no clinical significance, which would require further resources to investigate. We have not been able to estimate the magnitude of this problem, but it represents an additional source of saving from the intervention we performed.

Recently, a study from Vanderbilt University reported their experience of using a peer-management CPOE system based on a computerized multi-step intervention system (29). The first step of this system involved a query that asked providers if they wanted to discontinue tests scheduled beyond 72 hours. After this intervention, they then unbundled serum metabolic panel tests into single components, reducing the number of repeated targeted tests. This study reported a 24% decrease in the rate of ordering metabolic component panel tests.

This study is different from ours in two principal areas. First, the intervention on ordering did not come into effect until after the first 72 hours of admission. This would clearly not be of any value in the typical hospital setting in Israel, where the average stay in an internal medicine department is approximately 3.6 days. The system that we describe here came into effect immediately upon admission of the patient to the internal medicine department from the emergency room and did not require the establishment of any special software. In addition, the Vanderbilt study lasted 2 years, whereas ours lasted 3 years. Also, their comparison was made for tests ordered in different time periods—a baseline prior to the intervention and a period of follow-up extending slightly more than one year. There may have been other changes made in hospital procedure during this period that were not identified by the authors and that may have been confounding factors.

One strength of our study is that the comparison was made in real time between one internal medicine department and three others, all of which have approximately equal patient populations and an equal distribution of medical resources. This reduces the likelihood of confounding factors and makes the comparison more reliable.

The residents in the departments of internal medicine do not work on the day following a night on call. In addition, they do not work in the department for a full year of their 4-year residency, due to rotations to other specialties. Thus, there is a large mix of residents working in the department over a 3-year period. We could not obtain data on the number of tests ordered per physician, but we believe that this would be similar per time period. In addition, the number of tests ordered by a resident with his or her own signature decreases as he or she progresses through the residency—the actual signing for the tests is subsequently performed by the more junior residents. Thus, the total number of tests ordered by Department C is unlikely to be influenced by the actions of a specific physician.

A further possible benefit of this system, which we have not evaluated, is its the effect on the career-long ordering practices of the residents who are physicians-in-training. Residents in internal medicine programs gain permanent employment in many different sectors of medical practice. It is likely that test-ordering behavior that is acquired in the residency period will have a career-long impact, and that the effect of this behavior, spread over many years in many different clinical settings, could result in further significant savings.

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Comparative Radiologic Evaluation of Percutaneous Endoscopic Lumbar Discectomy and Open Microdiscectomy:

A Matched Cohort Analysis

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Abstract

Background: Only a few studies comparing percutaneous endoscopic discectomy and open discectomy have been reported in the literature. The purpose of this study was to compare the radiographic changes in patients treated with percutaneous endoscopic lumbar discectomy (PELD) with those of patients treated with open lumbar microdiscectomy (OLM).

Methods: A total of 30 patients who underwent PELD with a minimum three years of follow-up were randomly selected. To compare with the PELD group, 30 patients who underwent OLM during the same period were also randomly selected according to sex, age, and disc level. The clinical outcomes were evaluated by the Macnab criteria. Statistical analysis was performed using independent sample t-test, paired sample t-test, chi-square test, Fisher's exact test, and analysis of variance (ANOVA).

Results: The successful clinical outcomes were 96.7% in the PELD group and 93.3% in the OLM group. Among the various radiological parameters, changes of disc height (1.41 ± 1.19 mm in the PELD group and 2.29 ± 2.12 mm in the OLM group, $p=0.024$) and foraminal height (1.26 ± 0.91 mm in the PELD group and 1.85 ± 0.92 mm in the OLM group, $p=0.017$) were significantly different between the two groups.

Conclusions: Although the clinical outcomes were similarly satisfactory in both groups, PELD is a less invasive procedure than open microdiscectomy in selected cases.

Key Words: Intervertebral disc, herniated nucleus pulposus, lumbar microdiscectomy, minimally invasive surgery, endoscopy.

Introduction

Over the last six decades, many surgeons who have performed standard open discectomy for lumbar disc herniation have reported favorable clinical outcomes (1–3). However, there is always the risk of complications, such as intraoperative nerve root injury and postoperative perineural scarring and fibrosis (4–7). The postoperative disc space narrowing increases load transmission to the corresponding facet joints, leading to postoperative degenerative spondyloarthrosis and foraminal stenosis (8–10). Therefore, the symptoms may recur due to altered spinal geometry.

In order to overcome the drawbacks of open surgery and to accomplish direct removal of the pathological lesion while preserving the remaining normal disc, a number of minimally invasive spinal surgeries have been developed. Hijikata et al. introduced manual percutaneous nucleotomy in 1975 (11). Kambin et al. followed with the development of the posterolateral approach and instrumentation permitting removal of disc material with the aid of high negative pressure (12, 13). Subsequently, Onik et al. developed the nucleotome for automated percutaneous lumbar discectomy (14). Asher and Choy performed laser ablation of disc herniation in 1986 (15–17). In 1991, Kambin reported uniportal arthroscopic microdiscectomy, and Schreiber and Leu reported biportal lumbar nucleotomy (18, 19). In 1992, Mayer et al. introduced percutaneous endoscopic lumbar discectomy (PELD), combining forceps and laser (20). Knight et al., in 1998, reported percutaneous endoscopic laser foraminoplasty (21).

PELD is performed to remove the affected disc under local anesthesia while preserving normal structure as much as possible. The advantages of this procedure include a lower risk of facet joints

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injury, fewer postoperative complications, a shorter hospital stay and lower cost (13, 22, 23).

Only a few studies comparing percutaneous endoscopic discectomy and open discectomy have been reported in the literature. In 1993 Mayer and Brock compared the surgical technique and clinical results of percutaneous endoscopic discectomy with those of open lumbar microdiscectomy (OLM) (24). In 1999 Hermantin et al. compared the time to return to work and a satisfactory surgical outcome for open discectomy and video-assisted-arthroscopic microdiscectomy (25). However, until now, there has been no comparison study of the radiological changes and their relation to the clinical outcomes, for PELD and open microdiscectomy.

In this study, the authors compared the clinical and radiological outcomes of PELD and OLM. The radiological parameters such as disc height, foraminal height, disc signal intensity, subchondral marrow signal intensity, and facet joint osteoarthritis were evaluated.

Material and Methods

Patient Population

A total of 30 patients with a minimum of three years' follow-up in the PELD group were randomly selected from patients who underwent the procedure at the author's hospital between January and December 2000. To compare with the PELD group, 30 patients who underwent OLM during the same period were selected randomly according to sex, age, and disc level. The two cohorts were matched for these three criteria (Table 1). The inclusion criteria were as follows: (a) unilateral radicular leg pain rather than back pain, (b) soft lumbar disc herniations without stenosis, confirmed by both computed tomographic (CT) scan and magnetic resonance imaging (MRI), (c) patients without definite segmental instability, and (d) unsuccessful conservative treatment for at least three months.

The clinical outcomes were evaluated by the Macnab criteria (26). Statistical analysis was performed using independent sample t-test, paired sample t-test, chi-square test, Fisher's exact test, and analysis of variance (ANOVA). All p-values less than 0.05 were considered to be statistically significant.

All patients received x-rays, CT, and MRI preoperatively and at the last follow-up. The MRI was performed using Magnetom Symphony Ultragradient 1.5T MRI System (Siemens, Erlangen, Germany). Sagittal T1-weighted spin echo images were obtained with parameters of 550–750/12/2 (repetition time/echo time/excitations). Sagittal T2-weighted fast spin-echo images were obtained with parameters of 3500–4300/130–140/2. Fast low-angle shot (FLASH) axial images were obtained with parameters of 49/25/1 and flip angle of 30°. The section thickness was 1 mm, matrix size 256 × 512, and field of view (FOV) 260 mm. CT examination was performed on a Somatom Plus Sensation 4 scanner (Siemens, Erlangen, Germany). The disc height and disc height ratio were measured on plain lateral x-rays according to the modified Mochida's method (Fig. 1) (27). The foraminal height was measured as the maximum distance from the inferior margin of upper pedicle to the superior margin of lower pedicle (Fig. 2). Disc degeneration was classified into five grades on T2-weighted midsagittal images according to the grading system proposed by Thompson et al. (28). Degenerative changes of the subchondral marrow were evaluated on both T1- and T2-weighted MRIs by Modic's criteria (29). Facet joint osteoarthritis was divided into four grades on MRI and CT scans according to the grading system proposed by Fujiwara et al. (30). Two experienced radiologists independently evaluated all the radiographs.

TABLE 1
Patient Demographic Data

	PELD group (n=30)	OLM group (n=30)
Male: Female	22 : 8	22 : 8
Mean age	39.3 yr (range, 22–67 yr)	39.6 yr (range, 20–64 yr)
< 30	10	10
30–39	5	5
40–49	8	8
50–59	5	5
> 59	2	2
Operating level		
L4–5	24	24
L5–S1	6	6
Types of disc herniation		
Protrusion		
L4–5	8	8
L5–S1	1	1
Extrusion		
L4–5	16	16
L5–S1	5	5
Mean follow-up	38.2 mo (range, 32–45 mo)	36.8 mo (range, 35–42 mo)
Mean operating time*	42.6±14.21 min	65.1±23.17 min
Mean hospital stay*	19.5±30.12 hr	71.9±60.05 hr

* $p < 0.001$
PELD = percutaneous endoscopic lumbar discectomy; OLM = open lumbar microdiscectomy.

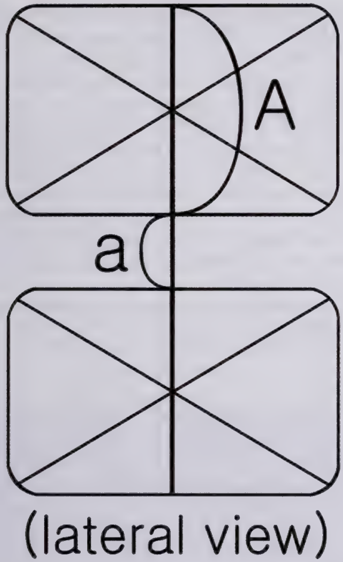

Fig. 1. Radiographic measurement of the disc height and disc height ratio. Disc height ratio was calculated by the following equation: a/A (at the final follow-up) × [a/A (at preoperation)]$^{-1}$.
a = disc height; A = vertebral height.

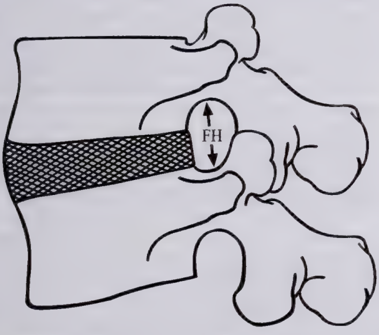

Fig. 2. Radiographic measurement of the foraminal height (FH). The foraminal height was measured as maximum distance between the inferior margin of pedicle of the superior vertebra and the superior margin of the pedicle of the inferior vertebra.

Surgical Technique

PELD was performed under local anesthesia with the patient awake and in a prone position. Fluoroscopic identification of the disc level was performed with the aid of a needle placed at the skin surface. After an 18G spinal needle was inserted into the disc space, an intraoperative discogram was obtained to identify the pathologic lesion in the lumbar disc. A thin guidewire then replaced the spinal needle and a small stab incision was made. The herniated fragment was removed by forceps, and the posterior annulus and disc tissues were vaporized by a Holmium-YAG laser or shrunken by a bipolar radiofrequency through the working channel under endoscopic visualization. Finally, complete decompression was confirmed intraoperatively through the endoscopic view.

OLM was performed as usual, using general anesthesia, with the patient in a prone position. After fluoroscopic confirmation of the disc level, a one-inch midline skin incision was made directly over the disc. Then the paraspinal muscle and soft tissues were retracted, and partial hemilaminectomy was performed with a high-speed drill. After removal of the ligamentum flavum, the nerve root was gently retracted and the herniated fragment was removed with an automated nucleotome and pituitary forceps, using an operating microscope.

Results

Clinical Outcomes

The demographic findings are presented in Table 1. The mean follow-up periods were 38.2 months (range, 32–45 months) in the PELD group and 36.8 months (range, 35–42 months) in the OLM group. The average operating time was 42.6 ± 14.21 min in the PELD group and 65.1 ± 23.17 min in the OLM group ($p<0.001$). The mean hospital stay was 19.5 ± 30.12 hours in the PELD group and 71.9 ± 60.05 hours in the OLM group ($p<0.001$).

According to the Macnab criteria, 24 (80.0%) patients had excellent results, 5 (16.7%) good, and 1 (3.3%) poor results in the PELD group. In the OLM group, 23 (76.7%) patients had excellent results, 5 (16.7%) good, and 2 (6.6%) fair results. Therefore, the successful outcomes were 96.7% in the PELD group and 93.3% in the OLM group. The one patient who achieved a poor result in the PELD group underwent subsequent open microdiscectomy because of an incomplete decompression.

Radiological Findings

Changes in disc height. In both groups, disc height and disc height ratio decreased during the follow-up period (Table 2). Overall, the mean disc height loss was 1.41 ± 1.19 mm in the PELD group and 2.29 ± 2.12 mm in the OLM group (p=0.024). The mean disc height ratio was 90.11 ± 9.86% in the PELD group and 82.75 ± 9.36% in the OLM group (p=0.004). Therefore, the postoperative disc space narrowing was lower in the PELD group than in the OLM group. There was no statistically significant correlation between disc height narrowing and ages in either group (Table 3). And there were no cases of postoperative instability in either group.

Changes in foraminal height. Foraminal height loss was observed in 16 patients in the PELD group and 25 patients in the OLM group. Overall, the mean foraminal height loss was 1.26 ± 0.91 mm in the PELD group and 1.85 ± 0.92 mm in the OLM group (p=0.017) (Table 2). The foraminal height loss was significantly proportional to the disc height loss in each group (p=0.017 in PELD group and p=0.019 in OLM group).

Changes in disc signal intensity. There were 14 cases (46.7%) showing disc signal change in the PELD group: six cases from grade II to grade III (five cases at L4–5 and one at L5–S1), two cases from grade II to grade IV (at L4–5), and six cases from grade III to grade II (five cases at L4–5 and one at L5–S1). There were 10 cases (33.3%) showing disc signal change in the OLM group: six cases from grade II to grade III (at L4–5 level), one case from grade III to grade IV (at L4–5 level), and three cases from grade III to grade II (at L4–5 level) (Fig. 3). The remaining cases had no intradiscal signal change. There was no statistically significant difference between the groups.

The mean grades of disc signal intensity decreased from 2.73 to 2.93 in the PELD group and 2.73 to 2.87 in the OLM group (p=0.211), with no statistically significant difference between the two groups (p=0.703). No clear correlation has been detected between clinical outcomes and changes of disc signal.

Changes in subchondral marrow signal intensity. There were eight cases (26.7%) showing subchondral marrow signal changes in the PELD group: normal to Modic type I in one case at L5–S1, normal to Modic type II in six (five at L4–5 and one at L5–S1), and Modic type II to Modic type I in one at L4–5. There were five cases (16.7%) showing subchondral marrow signal changes in the OLM group: normal to Modic type I in one case at L4–5 and normal to Modic type II in four (three at L4–5 and one at L5–S1). However, there was no statistically significant difference between the groups.

Osteoarthritic changes in the facet joint. There were three cases (10.0%) showing facet joint change in the PELD group: grade II to grade III in two and grade III to grade IV in one. In the OLM group, there were eight cases (26.7%) of the facet joint change: grade II to grade III in seven (six at L4–5 and one at L5–S1) and grade III to grade IV in one at L4–5 (Fig. 4). However, there was no statistically significant difference between the two groups (p=0.155).

Discussion

While open microdiscectomy is generally acknowledged as the standard of surgical treatment for a herniated lumbar disc, percutaneous endoscopic discectomy is now being performed with increasing frequency in technologically advanced nations. Although several studies involving this minimally invasive procedure have demonstrated clinical outcomes comparable to those of open microdiscectomy, data on long-term follow-up are few and the procedure's clinical applications are not established (31–33). In the present study, the authors compared radiologic changes as well as clinical outcome in patients treated with PELD and OLM.

The disc space narrowing after surgery was significantly lower in the PELD group (–1.41 mm)

TABLE 2
Changes in Disc Height, Disc Height Ratio, and Foraminal Height

Parameters	PELD group	OLM group	P-value
Preoperative disc height (mm)	10.90	10.50	
Postoperative disc height (mm)	9.49	8.21	
Loss of disc height (mm)	1.41	2.29	0.024
Disc height ratio (%)	90.11	82.75	0.004
Preoperative foraminal height (mm)	19.01	19.02	
Postoperative foraminal height (mm)	17.75	17.17	
Loss of foraminal height (mm)	1.26	1.85	0.017

PELD = percutaneous endoscopic lumbar discectomy; OLM = open lumbar microdiscectomy.

TABLE 3

Changes of Disc Height and Disc Height Ratio for Different Ages

Parameters	Age 20 (n=10)	30 (n=5)	40 (n=7)	50 (n=6)	60 (n=2)
PELD Group (n=30)					
Preoperative disc height (mm)	11.27	9.38	10.98	11.06	12.07
Postoperative disc height (mm)	9.6	7.77	9.67	10.35	10.47
Loss of disc height (mm)	1.67	1.61	1.32	0.72	1.60
Disc height ratio (%)	91.83	84.38	89.06	94.96	87.94
OLM Group (n=30)					
Preoperative disc height (mm)	10.71	9.95	11.32	9.91	9.66
Postoperative disc height (mm)	7.91	8.07	8.81	8.45	7.24
Loss of disc height (mm)	2.80	1.88	2.51	1.53	2.42
Disc height ratio (%)	80.03	84.40	85.39	86.48	73.83

PELD = percutaneous endoscopic lumbar discectomy; OLM = open lumbar microdiscectomy.

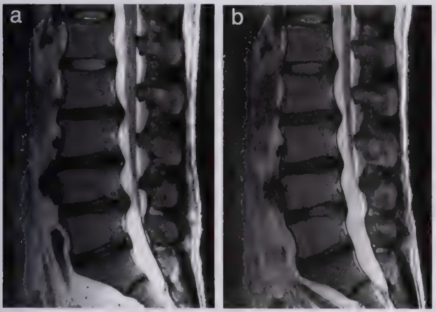

Fig. 3. Comparison of sagittal MR imaging in disc signal intensity. **(a)** Preoperative image demonstrating disc space with lower signal intensity (grade 3) at L4–5 level. **(b)** Postoperative image demonstrating disc space with more increased signal intensity (grade 2) after microdiscectomy.

than in the OLM group (!2.29 mm). The mean disc height ratio was 90.11±9.86% in the PELD group and 82.75±9.36% in the OLM group (p=0.004). These differences are thought to be due to the amount of disc removed and the resection of medial facet joint. Generally, the amount of disc removed during OLM is larger than that during PELD. Moreover, during open microdiscectomy, the medial portion of the facet joint is often partially removed to obtain enough exposure.

The degree of foraminal narrowing in the PELD group (–1.26 mm) was significantly lower than in the OLM group (–1.85 mm) (p=0.017). The difference is thought to be due to disc space narrowing and facet joint hypertrophy after surgery. Stephens et al. demonstrated that the normal foraminal height varies from 20–23 mm and that the foraminal narrowing may be exacerbated by loss of disc space (34). They also reported that the desiccation and degeneration of the superior articular processes of the inferior vertebra after disc space narrowing could lead to foraminal stenosis by an anterior-superior subluxation (34). In PELD, unlike OLM, damage to the facet did not occur and disruption of the central nucleus was minimal.

There are several reports of disc signal change and subchondral marrow abnormality after discectomy (35, 36). In this study, we observed the decrease of disc signal and subchondral marrow signal in some patients in both groups. This indicates that the postoperative degeneration may be accelerated by the disc removal, regardless of the type of operation. It is known that the postoperative signal changes could be caused by increasing of the axial loading after disc degeneration, discitis, or laser energy (36, 37).

The frequency of facet joint osteoarthritis was lower in the PELD group (10.0%) than in the OLM group (26.67%), with no statistically significant difference between the two groups. This difference may be caused by direct damage to the facet joint during OLM. However, because osteoarthritic changes of bilateral facet joints were observed in both groups, the authors assume that the cause of the facet joint osteoarthritis was the increased loading to the facet joint after surgery.

There was no significant difference in clinical outcome between the two groups. According to our results, the decompressive effect of PELD was comparable to that of OLM for patients with soft disc herniation without bony stenosis. The operating time and hospital stays in the PELD group were, however, much shorter than those in the OLM group. This result indicates that PELD is a less invasive procedure than OLM. Hermantin et al. also described arthroscopic discectomy as ef-

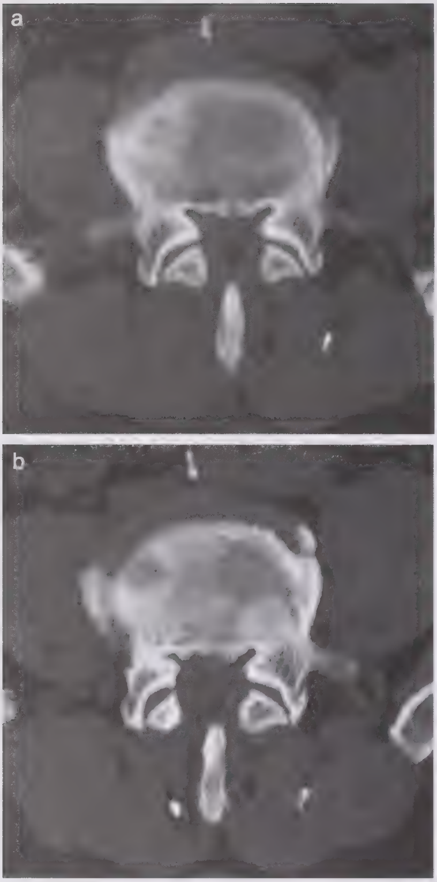

Fig. 4. Comparison of axial CT imaging in facet joint osteoarthritis. **(a)** Preoperative image demonstrating facet joints with grade 3 at L4–5 level. **(b)** Postoperative image demonstrating facet joints with grade 4 after microdiscectomy.

fective, with earlier return to work and less use of narcotics then open discectomy (25). Additionally, PELD is an outpatient procedure using local anesthesia. Thus, it can be effective for patients who cannot tolerate general anesthesia. Currently, most spinal surgeons have not been trained to perform PELD during their formal training period, so they have to learn the procedure on their own. There is a fairly steep and prolonged learning curve for this minimally invasive procedure. Therefore, the authors believe that minimally invasive endoscopic procedures should be performed by an experienced spinal surgeon with strict inclusion criteria.

Conclusion

Although the successful clinical outcomes were similar in the two groups, narrowing of disc height and foraminal height were lower in the PELD group than in the OLM group. Additionally, the operating time and hospital stays in the PELD group were much shorter than those in the OLM group. Therefore, this study suggests that PELD is a useful and less invasive procedure than open microdiscectomy for selected patients with lumbar disc herniation.

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A Comparison of Cardiologist and Noncardiologist Use of Echocardiograms:

Implications for Containing Health Care Costs

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Abstract

Echocardiography enables physicians to examine the heart noninvasively and provides a comprehensive evaluation of the cardiovascular system. However, because it is a relatively expensive procedure compared to an ECG or X-ray, it is crucial that "echo" be utilized appropriately and judiciously.

Using a retrospective chart review, we sought to determine whether there are differences in concordance between the diagnoses and echo findings of cardiologists and those of other physicians. Due to cardiologists' greater knowledge of cardiophysiology and echocardiography, cardiologists were expected to have a higher concordance between patient diagnosis and echocardiogram findings when compared to noncardiology physicians. Randomly, 500 echo reports were assessed for diagnosis, reason for the echo, and whether the echo findings agreed with the diagnosis. Other criteria that were studied included whether there were additional, unanticipated findings and whether these findings were of major or minor importance.

Concordance between cardiologist pre-test diagnosis and echo findings was found in 95 out of 175 tests (54%). Noncardiologist pre-test diagnosis concordance with echo findings was found in 117 out of 325 tests (36%) ($p<0.0001$). Thus, the cardiologists were found to have a significantly higher concordance between diagnosis and findings on echocardiogram when compared to noncardiologist physicians.

Key Words: Echocardiography, cardiology, health care costs.

Introduction

ECHOCARDIOGRAPHY is noninvasive and provides an efficient and accurate assessment of cardiac function, often able to provide unexpected findings that can alter both the diagnosis and course of treatment (1). According to one study, echocardiography provided 63.4% of all cardiovascular imaging for Medicare enrollees in 1998 (2). However, it is a relatively expensive procedure, contributing to rising health care costs.

The use of echocardiography continues to increase, and this technical procedure is ordered not only by cardiologists, but by internists and radiologists as well. But cost-effective test utilization requires an appreciation of the potential value of the exam as well as its accurate interpretation and appropriate integration into clinical care. Inappropriate or unnecessary use leads to increases in the cost of patient care and reduces the cost-effectiveness of this technology. In this study, we compared the degree of concordance between the clinical diagnosis and the echocardiographic findings for tests ordered by cardiologists and those ordered by noncardiologists. We hypothesized that cardiologists would have a greater concordance between their reason for ordering an echo and actual echo findings than noncardiologists.

Methods

We retrospectively reviewed random, non-sequential charts of patients who had had an M-mode, two-dimensional, and Doppler transthoracic echocardiogram (echo) during routine clinical care at a tertiary referral center in 2003. Both inpatients and outpatients were included. All studies were performed by registered technologists on state-of-the-art harmonic systems and read by level-3-trained cardiologists. Echoes of poor diagnostic yield due to inadequate imaging windows or incomplete echos were not included in this study. Echocardiograms of postoperative patients were included in this study to provide an accurate representation of physician-ordering patterns of transthoracic echocardiograms. Data were collected by a medical student uninvolved in patient

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care, employing a standardized form. Patient age and gender were recorded. Information regarding the pre-test diagnosis, the reason for performing the ultrasound, and the test findings were obtained from post-test echocardiographic reports written by a reviewing cardiologist. An independent cardiologist examined the concordance between pre-test diagnoses or reasons for performing an echocardiogram with test findings.

Physician pre-test diagnoses were considered accurate if test findings corresponded to the pre-test diagnosis and/or the reason for ordering the ultrasound. Significant echo findings were defined as any pathology severe enough to impact clinical management by a physician and patient. Insignificant findings included minimal valvular insufficiency or calcification, minimal pericardial effusions not affecting normal hemodynamics, ventricular ejection fractions above 55%, and minimal chamber dilatations. Additional test findings not predicted by pre-test diagnosis and/or reason for ordering echocardiogram were recorded and evaluated for significance, using the aforementioned criteria.

The results were blinded as to whether the ordering physician was a cardiologist or noncardiologist, a category which included a variety of physicians not specifically trained in cardiology, such as internists, emergency medicine physicians, surgeons and specialists in other areas of internal medicine. Concordance or substantial agreement between test findings and reasons for testing were tabulated and then separated into two groups, according to who ordered the test: cardiologists or noncardiologists. Category variables were evaluated using chi-square tests, and $p \leq 0.05$ was regarded as significant.

Results

We reviewed 500 random echocardiograms performed in 2003. The mean patient age was 63 years, with a median age of 64. There was no statistically significant age difference (N.S.) between the population referred by cardiologists (63.5) and that referred by noncardiologists (62.7). The average age when there was concordance of pre-test diagnosis and actual echo findings was 65.2; the average age when there was nonconcordance was 61.4 (N.S.).

The gender distribution of the patients referred by cardiologists and noncardiologists was similar. The gender distributions were also similar when tabulated according to pre-test diagnosis and reason for ultrasound. There was no significant relationship between gender and concordance of pre-test diagnosis and post-test findings.

The reasons for ordering an echocardiogram consisted mainly of assessments of ventricular and valvular function (107/500) (Fig. 1), problems with ventricular function only (237/500), and problems with valvular function only (58/500). However, the reason for ordering an echo did not compare with whether the test results subsequently agreed with the initial diagnosis.

Overall, physician pre-test diagnosis corresponded with actual test findings in 212 (42%) out of 500 total ultrasound exams. Concordance between cardiologist pre-test diagnosis and echo findings was found in 95 (54%) of 175 tests. Noncardiologist pre-test diagnosis concordance with echo findings was found in 117 (36%) of 325 tests (Fig. 2). Concordance rates between the cardiologists and noncardiologists were significantly different ($p<0.0001$).

Additional information unrelated to pre-test diagnosis and additional reasons for ultrasound as

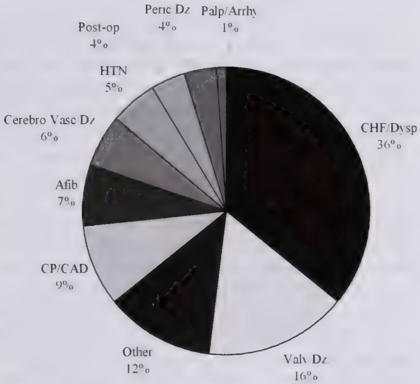

Fig. 1. Distribution of pre-test diagnoses.
HTN = hypertension; CP/CAD = chest pain / coronary artery disease; DZ = disease; CHF/Dysp = congestive heart failure / dyspnea; Afib = atrial fibrillation; Palp/Arrhy = palpitations / arrhythmia.

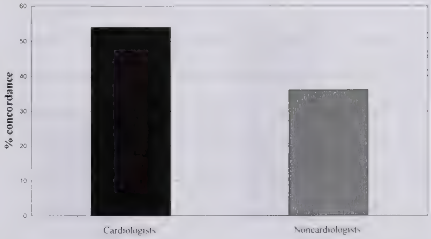

Fig. 2. Pre-test/post-test diagnosis concordance for cardiologists and noncardiologists ($p<0.0001$).

stated in echocardiographic post-test report were found in 273 of 500 exams. Additional information was obtained in 160 out of 325 echocardiograms (49.2%) ordered by noncardiologists, while further information was found in 113 out of 175 tests (64.5%) ordered by cardiologists. One hundred thirty-seven (50%) exams contained additional information of significant clinical importance. Major new findings were more frequent in echocardiograms ordered by the cardiologist group (38%) compared to the noncardiologist group (21.5%) (p=0.0114) (Fig. 3). Important additional information resulted most frequently from echocardiograms that were ordered for a pre-test diagnosis of congestive heart failure/dyspnea (40%), chest pain or coronary artery disease (10.3%), and valvular dysfunction (15.4%).

Discussion

Since its introduction, echocardiography has emerged as a leading diagnostic tool for patients with cardiovascular illnesses. However, the high cost of technology in medicine, including echocardiograms, mandates certain appropriate guidelines for its utilization. The balance between the benefit to patients, usefulness to health care providers, and cost may depend on appropriate usage and interpretation. In fact, Wann and Passo (3) argue that physicians' failure to interact with patients and provide adequate feedback to echo technicians may decrease the cost-effectiveness of this procedure. Concerns over health care costs have raised debates as to whether specialists or generalists order echocardiograms more appropriately. With no specialized training or certification needed to schedule an echocardiogram, tests may be ordered unnecessarily and therefore create an excessive burden on health care finances.

Previous investigators have explored differences in the way cardiologists and noncardiologists implement echocardiography to diagnose and treat cardiovascular disease. These studies have demonstrated that differences exist between these two groups, especially in terms of the age of the patients, the type of abnormality present, and the plan of action subsequently followed.

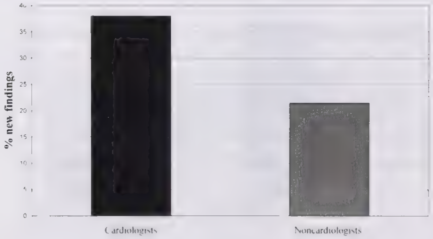

Fig. 3. Exam results with major new findings for cardiologists and noncardiologists (p=0.0114).

Comparisons between specialists and generalists have also been examined in other areas of internal medicine, and these studies have likewise shown differences between the two groups. For example, one study of asthmatic children demonstrated that even after adjustment was made for symptom severity, recent care encounters, and patient demographics, specialists were more likely than generalists to provide care that was consistent with national asthma guidelines (4). Another study examining how physician specialty affected the outcome of treatments for patients with diabetic ketoacidosis yielded similar results (5). The results showed that patients under the care of an endocrinologist had shorter hospital stays and incurred lower hospital costs than did patients whose physician did not have a subspecialty in diabetes.

One cardiological study demonstrated that in the treatment of unstable angina, internists were less likely to use aspirin, heparin, and beta-adrenergic blocking agents in their initial treatment (6). The mortality rate of patients cared for by internists was higher, suggesting that these patients did not receive the most effective medical therapy.

A study by the Pennsylvania Health Care Cost Containment Council suggests that care provided by cardiologists might not only be superior to that provided by generalists, but might even be more cost-effective. The council examined the clinical and administrative data on 40,684 hospital admissions for acute myocardial infarction in Pennsylvania in 1993 and determined that patients cared for by cardiologists had a lower risk-adjusted mortality rate and shorter length of stay than did patients cared for by internists or family practitioners (7).

A study published in 1999 found that cardiologists were more aggressive than internists in ordering echocardiograms to test both aortic stenosis and mitral regurgitation (8). Cardiologists often would order echoes for patients who were asymptomatic, whereas internists would wait until the disorder was significantly more severe before they ordered imaging studies. However, the study also pointed out that the higher costs could be balanced by lower morbidity and mortality rates resulting from an earlier diagnosis.

Another study showed that cardiologists tended to order echoes for an older patient population and used this technology as a means of determining left ventricular dysfunction and detecting wall motion abnormalities (9). Internists, in contrast, ordered echocardiograms for younger patients and focused more on detecting valvular heart disease, a cardiac source of embolism, and vegetation in patients with suspected endocarditis. A change in management that resulted from echo findings also occurred more frequently where cardiologists ordered the test.

In this retrospective chart review study, we attempted to assess whether the ordering of echocardiography by noncardiologists might be less cost-effective by comparing the accuracy of the diagnoses predicted by cardiologists with those predicted by noncardiologists prior to the echocardiogram. In this study, no significant age difference was found between populations referred by cardiologists and by noncardiologists. There was also no significant difference in the gender of these populations. Our study further revealed that echocardiograms were ordered most often to evaluate ventricular dysfunction, valvular dysfunction, or both.

Our results showed that cardiologists' pre-test patient diagnoses and reasons for testing corresponded with echo results more often than those of noncardiologists (54% to 36%, $p<0.0001$). Also, echocardiograms ordered by cardiologists revealed additional information more frequently than those ordered by noncardiologists. Furthermore, clinically significant additional information resulted more often from tests ordered by cardiologists. Pre-test diagnoses of congestive heart failure or dyspnea, chest pain or coronary artery disease, and valvular dysfunction most frequently resulted in echocardiograms that provided major additional information.

There are several significant limitations to the results of our study. As mentioned before, the data gathered for this study came from a retrospective chart review. Retrospectively, we cannot know the precise reason for ordering an echo other than the written diagnosis and purpose of the exam. Furthermore, the effectiveness of an echocardiogram in clinical practice is determined by its impact on subsequent patient management, which we did not determine.

Another limitation is our inability to know the true intent of the physician ordering the echo; was it to confirm suspected or known disease, or because of a clinical dilemma? Because we could not interview the physician or the patient, it may be difficult to gauge the true purpose of the request. Moreover, any small-sample size error might affect our data's applicability to a wider population and we did not determine if the generalists gained more then the cardiologists by the echo results. The echoes they ordered confirmed the cardiologists' suspicions, by elucidating the severity of an entity, but those same tests might have proved even more valuable than to the noncardiologists, who might not have diagnosed certain abnormalities without the echocardiogram.

Conclusion

Our study showed that cardiologists are more accurate than generalists (54% to 36%, $p<0.0001$) in their use of echocardiography, meaning that their predicted diagnoses were confirmed more often by echocardiogram than those of noncardiologists. This could have important implications in the management and treatment of cardiovascular disease. Since the number of people who suffer these illnesses is likely to increase over the years, medical costs will probably continue to rise also. Efforts to contain these costs could be affected by who is allowed to order echocardiograms. Because this procedure is expensive, it might be more cost-effective if only cardiologists were able to order echocardiograms, since they have more experience and knowledge and would know the circumstances that would truly warrant the use of echocardiography. However, our study is a preliminary one. Further investigations are needed to see whether these trends are applicable to larger populations.

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Tuberculosis of the Aryepiglottic Fold and Sinus Pyriformis:

A Rare Entity

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Abstract

Tuberculosis of the larynx and hypopharynx is an uncommon entity and rarely considered in the differential diagnosis of the laryngo-pharyngeal diseases. We describe a case of a 40-year-old man with tuberculous involvement of the aryepiglottic fold and medial wall of the sinus pyriformis mimicking a malignancy. Current literature concerning the clinical, histopathological, radiological and diagnostic features of this rare entity is discussed.

Key Words: Larynx, hypopharynx, sinus pyriformis, tuberculosis, diagnosis.

Introduction

According to World Health Organization (WHO) statistics, each year approximately 10 million people worldwide contract tuberculosis, mainly involving the lung, and more than 3 million people die from the disease (1, 2). In Turkey, the number of people infected with tuberculosis yearly is estimated to be about 35,000–40,000 (2). Mycobacterial disease is also increasing in most of the industrialized countries (3). This increase may be due to several factors: the HIV epidemic, immigration from countries where tuberculosis is endemic, transmission of tuberculosis in crowded settings, deterioration in quality of health care, and immunosuppressive drugs (2, 3). The tuberculosis bacilli that cause disease in humans are generally *Mycobacterium tuberculosis*, *M. bovis* and *M. africanum*. Humans are the only reservoir for *M. tuberculosis*. Mycobacterial infections are usually classified into two groups: (a) infections caused by *M. tuberculosis*, and (b) infections caused by the atypical mycobacterial organisms (4).

Laryngeal tuberculosis was the most common disease involving this anatomical region in the early part of the twentieth century (5). However, today laryngeal involvement is extremely rare (6). This report describes a case with the unusual submucosal presentation of tuberculosis in the medial wall of the pyriform sinus and aryepiglottic fold of the larynx, with clinical mimicking of malignancy.

Case Report

A 42-year-old male patient was referred to our department in order to rule out carcinoma of the larynx and hypopharynx. He had been evaluated by a physician because of a 2-month history of difficulty and pain in swallowing. Magnetic resonance imaging (MRI) of the neck revealed a left-sided laryngo-hypopharyngeal mass involving the pyriform fossa. The aryepiglottic fold of the larynx presented a low-intensity in a T1-weighted image and a high-intensity in a T2-weighted image (0.5 Tesla open MRI view) (Figs. 1A and 1B).

The patient was a heavy smoker and had worked in a cement factory for 20 years. In our examination, indirect laryngoscopy showed a marked submucosal edema in the left pyriform sinus and aryepiglottic fold. There was no superficial ulceration. The epiglottis, false and vocal folds were not affected. There were no palpable cervical lymph nodes. The rest of the ear-nose-throat and physical examinations were normal. Chest radiography,

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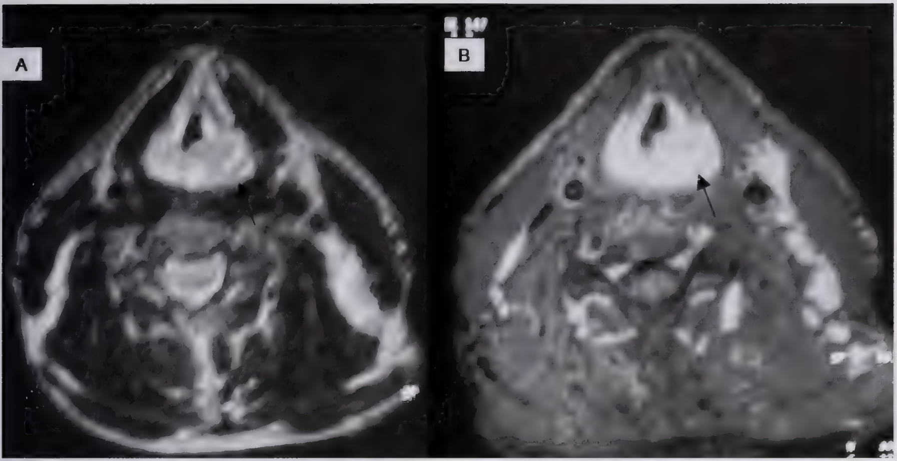

Fig. 1. MRI view of the tuberculous lesion (arrow indicates the tuberculotic involvement of the left-sided aryepiglottic fold and medial wall of sinus pyriformis). **(A)** T_1-weighted view, **(B)** T_2-weighted view.

however, revealed an apical infiltration in the right upper lobe of the lung (Fig. 2). A complete blood count was unremarkable, and erythrocyte sedimentation rate was slightly higher than the normal limits. HIV serology was also negative. A purified protein derivative test was not diagnostic due to prior vaccination. A direct laryngoscopy was performed using general anesthesia, and multiple submucosal biopsy specimens were taken from the pyriform sinus, aryepiglottic fold, post-cricoid and cervical esophageal regions. Pathologic examination revealed tuberculoid-type granulomas with areas of caseation necrosis, epithelioid cells, lymphocytes and Langhans' type giant cells (Fig. 3). Sputum culture was positive for acid-fast bacilli. On the basis of the bacteriologic, radiologic and histopathologic findings, the diagnosis of pulmonary tuberculosis with larynx and hypopharynx involvement was established. A standard 6-month treatment with a combination of isoniazid, rifampicin, pyrazinamide, and ethambutol was started. The follow-up after treatment showed resolution of the symptoms, and 6 weeks later an MRI confirmed the improvement of the mass (1.5 Tesla MRI view) (Fig. 4).

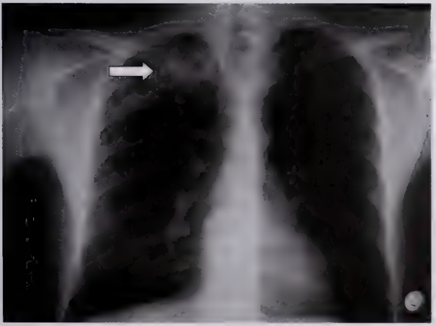

Fig. 2. Chest X-ray reveals an apical infiltration (arrow) in the right upper lobe of the lung.

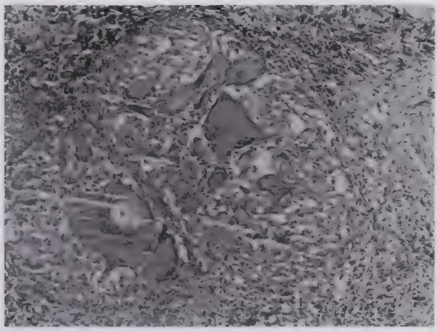

Fig. 3. Microscopically, non-necrotizing and necrotizing granulomas with Langhans giant cells and dense mononuclear inflammatory cell infiltration were seen under the squamous epithelium (HE, ×200).

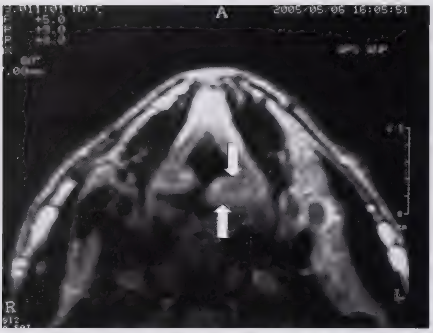

Fig. 4. Post-treatment MRI view of the lesion reveals a marked improvement of the lesion. Arrow indicates that minimal edema of the left aryepiglottic fold still persists.

Discussion

At the beginning of the 20th century, laryngeal tuberculosis was the most common disease of the larynx, but by the 1980s, this entity had become extremely rare, especially in developed countries (7). However, during the past decade, the incidence of laryngeal tuberculosis has increased and gained much attention for three important reasons: (a) many physicians do not consider tuberculosis in the differential diagnosis of laryngeal lesions and symptoms; (b) the disease has changed its behavior, targeting new age groups and sites with new types of lesions, including the presence of concomitant pulmonary lesions, (c) HIV and other immunosuppressive diseases and treatments have increased in the clinical setting (7).

Tuberculosis of the upper aerodigestive tract is a rare clinical entity, and recent incidence of laryngeal tuberculosis is less than 1% of all tuberculosis cases (2, 8). Rohwedder found only 11 laryngeal cases (1.3%) in his series of 843 tuberculosis patients (9).

The pathogenesis of laryngeal involvement is either primary or secondary (10, 11). Primary lesions occur in the absence of pulmonary disease. There are two theories for the etiopathogenesis of laryngeal tuberculosis: (a) the bronchogenic theory, which states that laryngeal involvement is secondary to pulmonary disease (directly spread) and (b) the hematogenous theory, which states that the larynx is infected from sites other than the lungs (12). In the present case, the laryngeal involvement was probably secondary to pulmonary disease.

The ratio of male to female patients with epiglottic tuberculosis is 2:1 to 3:1, and according to recent series, its predominant occurrence in individuals from 40–60 years of age (13). The age of the present case (42 years old) was in this age range, but slightly lower than the reported average age, and the main risk factors were probably previous pneumoconiosis and smoking habit.

The most common clinical presentations of patients with tuberculosis are hoarseness (80–100%), dysphagia and odynophagia (50–67%), cough (44–48%), dyspnea (25%), hemoptysis (18–29%), cervical lymphadenopathy (12%), weight loss, and (rarely) systemic dissemination (11–13). In the present case, the main symptoms were dysphagia and odynophagia.

Classically, laryngeal involvement is mainly in the posterior half of the larynx, due to pooling of the infected sputum (7). However, according to Cleary and Batsakis, localization in the anterior half of the larynx now occurs twice as often as in the posterior half, and vocal cords are the most commonly affected site (50–70%), followed by false cords (40–50%), and epiglottis, aryepiglottic folds, arytenoids, posterior commissure and/or subglottis (10–15%) (3). Also, Gallas et al. reviewed 738 cases of laryngeal tuberculosis in articles in English and French. Of those 738 cases, 60.5% had localization in only one region of the larynx, most frequently the vocal cords (14). In the present case, the medial wall of the pyriform sinus and aryepiglottic fold were involved.

Classic signs of laryngeal tuberculosis are localized edema, granuloma or ulceration (12, 15). However, recent series have demonstrated that the appearance of edematous, polypoid laryngitis that is not easily distinguished from chronic laryngitis is increasing. According to Shin et al., the findings of laryngeal tuberculosis may be categorized into four groups: (a) whitish ulcerative lesions (40.9%), (b) nonspecific inflammatory lesions (27.3%), (c) polypoid lesions (22.7%), and (d) ulcerofungative mass lesion (9.1%) (16). We suggest that the present case involved one of the nonspecific inflammatory lesions (localized edematous mucosal appearance). Mucosal edema is probably secondary to lymphatic obstruction by the granulomas (6).

The diagnosis of tuberculosis can be established with a history, PPD test, chest X-ray, acid-fast sputum smears, bacteriological culture, and histopathology. Computerized tomography and MRI can show typical signs, such as mucosal lesions without infiltration of cartilaginous or prelaryngeal areas and paralaryngeal fat (13). In the present case, MRI revealed a "mucosal lesion" rather than an infiltrative tumoral lesion. Histopathologic examination of the lesion is the cornerstone of an appropriate diagnosis. Epithelioid granuloma with Langhans type giant cell, granulomatous inflammation and caseating granuloma formation are characteristic features of this form of tuberculosis (8). It should be kept in mind that both tuberculosis and malignancy may coexist in the same patient (11). Therefore, the diagnostic challenge is, as in our case, first to exclude a laryngeal cancer. Other differential diagnostic considerations include syphilis, sarcoidosis, Wegener's granulomatosis, fungal infections, actinomycosis, leprosy, systemic lupus erythematosus, rheumatoid arthritis, relapsing polychondritis and amyloidosis (11).

An antituberculous therapy offers a good prognosis, generally curing the disease without any sequela. Most lesions disappear over a 2-month period, as in the present case.

Conclusion

Today, otorhinolaryngologists should be aware of a tuberculotic lesion in the differential diagnosis of the various head and neck pathologies. The incidence of tuberculosis is increasing worldwide, and the disease has changed its behavior in several ways. Tuberculosis of the larynx and hypopharynx should be suspected in cases presenting with dysphagia and odynophagia mimicking a laryngo-pharyngeal carcinoma.

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Aortic Occlusion in Patients Treated with Cisplatin-Based Chemotherapy

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Abstract

Cisplatin-based chemotherapy is one of the most common chemotherapy regimens that is complicated by thromboembolic events. A wide spectrum of vascular events exists, including venous and arterial thromboses of varying severity and location. However, total occlusion of the aorta is very unusual. We describe two patients with atherosclerotic vascular disease who developed occlusion of the abdominal aorta after cisplatin-based chemotherapy.

Key Words: Cisplatin-based chemotherapy, thrombosis, aorta, peripheral vascular disease.

Introduction

Patients with cancer have a highly increased risk of thrombotic events, with venous thrombosis far more common than arterial thrombosis. However, compared to venous thrombosis, arterial vascular events are more likely to be life or limb threatening. A number of chemotherapeutic medicines have been associated with an increased rate of thromboembolism. Anti-cancer drugs known to cause vascular events include platinum-based compounds, vinca acaloids, bleomycin, dacarbazine, L-asparaginase, tamoxifen, and diethylstilbestrol. The wide spectrum of arterial and venous thromboembolic events are well-known complications of cisplatin-based chemotherapy, but total aortic occlusion is very uncommon. We present two patients with known atherosclerotic disease who developed total occlusion of the abdominal aorta following cisplatin-based chemotherapy.

Case 1

A 52-year-old female presented with poorly differentiated gastric adenocarcinoma with liver metastases. Her history was remarkable for insulin-dependent diabetes mellitus, hypertension, hyperlipidemia, smoking and ischemic heart disease. Her chronic medications were aspirin, atenolol, slow-released nefedipine, simvastatin and valsartan. The patient received chemotherapy consisting of cisplatin 75 mg/m^2 intravenously on day 1; 5-fluorouracil 1200 mg/m^2 as continuous intravenous infusion; and 5-fluorouracil 400 mg/m^2 as intravenous bolus and leucovorin 200 mg/m^2 on days 1, 2, 15, and 16. On day 18 of the chemotherapy cycle, the patient developed paresthesias of both legs and buttock pain. After a few hours her legs were cold, painful, pale and weak. No femoral, popliteal or distal foot pulses were detected. Doppler study showed occlusion of the aorto-iliac segment with total lack of blood flow to the legs. A clinical diagnosis of aortic occlusion with bilateral leg ischemia was made, and subcutaneous low-molecular-weight heparin (LMWH), enoxaparin, was started. A computed tomography (CT) scan showed thrombosis of the aorta immediately below the level of the renal arteries, and thrombosis of both common and external iliac ar-

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teries with open femoral arteries. The patient's poor general condition, due to extensive metastatic disease, precluded surgical intervention and thrombectomy. She remained in the hospital and subsequently expired.

Case 2

A 57-year-old female was investigated for chest pain and hyponatremia. She had a history of smoking, hyperlipidemia and ischemic heart disease, with myocardial infarction two years earlier. She was being treated with simvastatin and aspirin. A CT scan revealed a left lower lobe mass and multiple liver lesions. A transbronchial biopsy identified the mass as small-cell lung cancer. The patient received four cycles of chemotherapy using cisplatin 80 mg/m? intravenously on day 1 of the cycle and etoposide 100 mg/m^2 intravenously on days 1–3; this was repeated every 21 days. Three days after completion of the fourth cycle of chemotherapy, the patient developed numbness in her left hand and left foot. The next day she was admitted to the hospital with severe pain in her back and both legs. The neurological examination was normal. Spinal cord compression was suspected, but a CT scan of the head and spine was normal. During the next 24 hours the patient developed cyanosis of both feet. Doppler study showed occlusion of the aorto-iliac segment and stenosis of calf arteries bilateral with ankle-brachial indexes of 0.32 and 0.11 in the right and left sides, respectively. A CT scan showed saddle thrombus beginning 3 cm above the aortic bifurcation (see Figure). Subcutaneous enoxaparin (LMWH) was started, and the patient underwent bilateral transfemoral thrombectomy. A repeat Doppler study, performed 5 days after the operation, revealed stenosis of the right calf arteries with ankle-brachial indexes of 0.76 and 1.2 in the right and left sides, respectively. Enoxaparin was continued. The chemotherapy regimen was changed to carboplatin and etoposide. Two months after surgery the patient was free from peripheral vascular disease symptoms, and the ankle-brachial index was 0.75 in each leg.

Discussion

Cisplatin-induced thromboembolic events are well-known and widely described complications of cisplatin-based chemotherapy. Several hypotheses have been proposed to explain the occurrence of venous and arterial complications in patients treated by cisplatin-based chemotherapy, including hypomagnesemia, damage of the vascular endothelium, and elevated von Willebrand factor plasma levels (1). A wide spectrum of vascular events exists, including venous and arterial thrombosis of various severities and locations. However, total occlusion of the aorta is very unusual, and only two cases have been described previously (2) Our patients had multiple risk factors for cisplatin-induced complications, including evidence of widespread atherosclerotic disease, liver metastases, hypomagnesemia and antiemetic therapy with dexamethasone. Both patients developed total occlusion of the abdominal aorta and were treated with low-molecular-weight heparin (enoxaparin), and one of them underwent surgical revascularization.

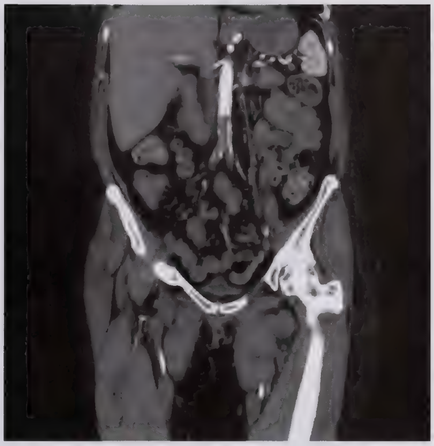
Figure. A contrast enhanced coronal CT section shows saddle thrombus beginning 3 cm above the aortic bifurcation.

There are a few published studies concerning the incidence of vascular complications of platinum-based chemotherapy.

Weijl et al. (1) performed a retrospective study of 179 patients who received a cisplatin-containing regimen for germ-cell cancer. Eighteen vascular events occurred in 15 patients (8.4%), including three arterial events. Liver metastases and the administration of ≥ 80 mg dexamethasone per cycle as antiemetic therapy were risk factors for the development of major thromboembolic complications.

Numico et al. (3) recently evaluated major vascular events in 108 patients with non-small-cell lung carcinoma treated with cisplatin and gemcitabine chemotherapy. Overall, 22 vascular episodes occurred in 19 patients (17.6%), including 10 arterial events (2 myocardial infarctions, 7 lower limb arterial thromboses, 1 ischemic stroke) and 12 venous thromboemboli. Four patients died due to the vascular events and 3 patients required surgical revascularization.

In a retrospective study of 263 patients who received cisplatin as part of chemotherapy for urothelial cancer, Czaykowski et al. found a 12.9% incidence of vascular events with a 4.1% incidence of arterial thrombosis (4).

Mathews et al. (2) described 5 patients who received chemotherapy with combinations containing cisplatin or carboplatin for lung cancer, and developed arterial thrombosis soon after initiation of treatment. Cardiovascular risk factors, such as hyperlipidemia, hypertension, diabetes mellitus, smoking and preexisting arterial disease, were detected as important risk factors for the development of arterial thrombosis. In this study, two cases of aortic occlusion were described. One patient underwent thrombectomy of the aorta with aortobifemoral grafts and was free from vascular symptoms three years after the operation. A second patient underwent axillary bifemoral grafting and developed a recurrence of leg ischemia after cisplatin with etoposide chemotherapy one year later. He underwent thrombectomy of one of the axillofemoral grafts.

Since cisplatin-induced thromboembolic events are not rare, we suggest that preventive anticoagulation during and a few days following the administration of cisplatin-based chemotherapy may be effective in patients with multiple risk factors for vascular events.

Use of preventive anticoagulation in cancer patients at high risk of thrombosis is not new in oncology. Very-low-dose warfarin has proven to be effective in patients with metastatic breast cancer receiving chemotherapy (5). LMWH (nadroparin) at a fixed, prophylactic dose and warfarin at a fixed, very low dose had a similar benefit-to-risk ratio and lowered the risk of adverse events in the prevention of thrombosis associated with central venous catheters in cancer patients (6). Although interaction between warfarin and cisplatin has not been reported in the literature, use of warfarin with other chemotherapeutic drugs (5-fluorouracil or etoposide) commonly given in combination with cisplatin may alter the metabolism and anticoagulant effect of warfarin (7, 8). We suggest that preventive anticoagulation by LMWHs may be more effective and safer.

However, further prospective studies are needed to confirm the possible effectiveness of LMWH in preventing vascular events in cancer patients receiving platinum-based therapy.

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The Diagnostic Value of QT Dispersion for Acute Coronary Syndrome in Patients Presenting with Chest Pain and Nondiagnostic Initial Electrocardiograms

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Abstract

BACKGROUND: Patients presenting with chest pain and nondiagnostic electrocardiograms (ECG) in the emergency department (ED) often pose a challenge to physicians. QT dispersion (QTD) is an electrocardiographic marker of myocardial ischemia due to nonhomogeneous ventricular repolarization. We hypothesized that QTD could accurately identify patients with acute coronary syndrome (ACS) who presented with chest pain and nondiagnostic initial ECGs.

METHODS: All patients admitted to the ED with chest pain and nondiagnostic initial ECGs were included in the study prospectively. QTD and QTc dispersion (QTcD) were measured at the initial ECGs and compared for ACS patients vs. non-ACS patients. A receiver operating characteristic curve was drawn to evaluate the diagnostic value of QTD and QTcD for ACS.

RESULTS: Of the 137 patients with an initially nondiagnostic ECG, 51 were finally diagnosed with ACS (37%). Mean QTD and QTcD of patients with ACS were significantly greater than those of patients without ACS (39.61±12.9 vs. 32.56±15.1, $p=0.004$; 46.12±16.3 vs. 38.10±18.2, $p=0.009$, respectively). The area under the curve was 0.624, $p=0.015$ for QTD, and 0.603 and $p=0.049$ for QTcD. When various cut-off points were evaluated, potentially useful values were determined between 30 and 50 ms for QTD (sensitivity 86% and 10%, specificity 35% and 97%, respectively). These values were 40.5 and 49.5 ms for QTcD (sensitivity was 96% and 32%, specificity was 12% and 77%, respectively).

CONCLUSION: For patients with chest pain and nondiagnostic initial ECG, ACS risk is high if QTD and QTcD values are greater than 40 ms. Therefore, QTD and QTcD can help identify patients with acute coronary syndrome who present with chest pain and a nondiagnostic initial ECG. However, poor operator characteristics of QT dispersion could limit its value as a diagnostic test in the clinical setting.

Key Words: Chest pain, QT dispersion, emergency department, nondiagnostic electrocardiogram, acute coronary syndrome.

Background

CHEST PAIN is a frequent cause for admission to the emergency department. It can be a sign of various conditions, from a minor disorder to a life-threatening disease such as acute myocardial infarction (AMI) (1). It is crucial for the physician to diagnose acute coronary syndrome correctly for the patient admitted to the ED with chest pain. (Patients with chest pain comprise 5–20% of all ED presentations [2, 3]). A majority of the patients presenting with chest pain are usually admitted to the hospital for further evaluation and management, but studies indicate that some 60% are discharged with a diagnosis other than ACS. Despite the availability of modern-day tools for diagnosis of AMI, about 5% of patients with AMI are missed in the ED, with subsequent associated morbidity and mortality, as well as legal consequences. So, patients with low AMI risk must be observed in the ED for a period of time and discharged if clinical features and cardiac markers warrant it, in order to decrease the cost and duration of hospitalization (4).

Since the beginning of the 20th century, the electrocardiogram has been used widely for diagnosis and patient follow-up. Of the patients with classical ECG findings, such as new Q wave development or ST segment changes, 75–86% have been diagnosed with AMI, while only 40–65% of the AMI patients and 10% of unstable angina pectoris (UAP) patients have displayed these classical findings in their initial ECG (5, 6).

The QT interval represents the total duration of ventricular depolarization and repolarization. In

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1990, Day et al. (7) named the difference in the QT intervals between the derivations from ECG leads as "QT dispersion" (QTD) and noted that it represents the degree of the repolarization heterogeneity. "QTD" is defined as the difference between the maximum and minimum QT intervals, occurring in any of the 12 leads. Prolonged QTD is associated with an increased risk of serious ventricular arrhythmias in patients with long QT syndrome, hypertrophic cardiomyopathy, chronic heart failure or myocardial infarction (8). Experimental work has shown that increased dispersion of electrical recovery after activation is a key factor in the development of serious and fatal arrhythmias associated with ischemia (9).

In the United States each year, more than 5.3 million individuals present to emergency departments with chest discomfort and related symptoms. Ultimately, more than 1.4 million people are hospitalized for unstable angina and non-ST-segment elevation myocardial infarction. For emergency physicians and cardiologists alike, these patients represent an enormous challenge to accurately diagnose and appropriately treat. Identifying patients with ACS presenting to the ED is vital, and so it is critical to perform risk stratification early in the course of a patient's evaluation. The history, including risk factors for coronary artery disease development, as well as the physical examination, helps the clinician to screen patients for ACS. The 12-lead ECG and cardiac biomarkers serve as the major ancillary testing tools for risk stratification in the emergency setting (10). Yet despite all efforts to identify ACS, missed diagnosis is a continuing challenge. Discharging patients with acute myocardial infarction or unstable angina from the ED because of missed diagnoses can have dire consequences.

It has been suggested that QTD is a useful indicator for ischemic heart disease diagnosis and that it will reach the highest level in the first hours following AMI but may still be high when compared with healthy controls (11). The aim of this study was to assess the use of QTD and QTc dispersion (QTcD) to predict the likelihood of ACS in patients who present to the ED with chest pain and nondiagnostic initial ECG.

Material and Methods

The study was conducted at Firat University, Department of Emergency Medicine, between June and November 2002. Included in the study were patients with chest pain and without diagnostic initial ECG findings indicating ACS on ED presentation. Each patient was placed on a cardiac monitor and a standard 12-lead ECG with a paper speed of 25 mm/s was taken. Patients' age, gender and time of pain onset were recorded. One copy of all initial ECGs of patients with chest pain was collected for the study. A single attending emergency physician and a cardiologist interpreted the initial ECGs without knowing the clinical presentation. All patients with nondiagnostic ECGs were included in the study.

Diagnosis of ACS

All study patients were examined and treated according to the usual practice. Diagnosis was based on final hospital discharge. Diagnosis of ACS (as per our institution's protocol) was based on ACS-specific special ECG changes in typical clinical features. In addition, serum markers were evaluated for indications of cardiac damage: specifically, initial cardiac troponin-T (cTn-T), creatine kinase myocardial band (CK-MB), and myoglobin levels were measured initially and repeated after the 6th hour. If the result was positive, samples were taken at six-hour intervals for 48–72 hours.

Determination of Myocardial Necrosis

1. Serial increase in plasma CK-MB level (more than 25% increase between two measurements).
2. CK-MB to total CK rate over 5%.
3. After 12 hours, cTn-T value over 0.1 ng/mL.

Evaluation of Serum Samples

Quantitative serum CK-MB and myoglobin level measurements were made with Cobas Integra-800 autoanalyzer (Roche Laboratory Systems, Mannheim, Germany) in the biochemistry laboratory. cTn-T levels were measured with Cardiac Reader (Roche Laboratory Systems) at bedside. Normal levels were 0–25 mg/dL for CK-MB, 7–76 mg/dL for myoglobin, and 0–0.10 ng/mL for cTn-T.

Measurement of QT and QTc

Excluded from the study were patients with any of the following: ECGs with diagnostic features for ACS, unclear QT interval in at least seven ECG leads, bigeminal ventricular systole, atrial fibrillation, a pacemaker, or current drug use affecting QT interval. QT interval was calculated from the onset of the QRS complex to the point of return of the T wave to the isoelectric line. Three sequential complexes were measured and the mean value was used for QT interval calculation. For the patients with biphasic T waves, the intersection point of downstroking maximum T wave curve and the line tangential to isoelectric line was accepted as the end point. If there was a U wave, the lowest point between the two waves was accepted as the end point of the T wave (1). The difference between the maximum and minimum QT intervals, occurring in any of the 12 leads, was measured as QTD. QTc max and QTc min were determined with the Bazett formula (QTc= QT / $\sqrt{RR}$), and the difference between QTc max and QTc min was calculated as QTcD (12).

Quantitative data were reported as mean ± standard deviation and qualitative data were reported as percentages. Differences in continuous variables (QTD and QTcD) were assessed using a 2-tailed Student's t test. Additionally, differences in the covariates of interest (gender and history of myocardial infarction) were assessed using the Mann-Whitney U test and chi square test, where appropriate for the patients with and without ACS. A p value <0.05 was considered to indicate statistical significance. Agreement between observers was verified using the Bland-Altman method (13). To evaluate the diagnostic value of QTD and QTcD for ACS, a receiver-operating characteristic (ROC) curve was created and the area under the curve (AUC) was calculated. The data were analyzed in the SPSS 11.0 program (SPSS Inc., Chicago, IL).

Results

During the study period, 232 patients with chest pain were admitted to the ED. A total of 95 patients were excluded (41%) from the study; 21 of the patients (9%) were excluded because QT measurements were not obtained or QT interval was affected by drugs or pacemaker. Of the 137 studied patients, 51 had ACS (37%). ST-segment elevation myocardial infarction (STEMI), non-STEMI, and UAP were diagnosed in the ACS group during follow-up period (n=4, 3, and 44, respectively; Fig. 1). Demographic features of the groups are shown in the Table. The mean difference between observers in the measurement of QTD and QTcD (n=30) was 0±5 ms and 0±4 ms; 95% CI was between –1 and 1 ms respectively.

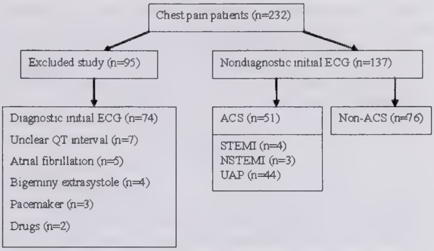
Chest pain patients (n=232)
Excluded study (n=95)
Nondiagnostic initial ECG (n=137)
Diagnostic initial ECG (n=74)
Unclear QT interval (n=7)
Atrial fibrillation (n=5)
Bigeminy extrasystole (n=4)
Pacemaker (n=3)
Drugs (n=2)
ACS (n=51)
STEMI (n=4)
NSTEMI (n=3)
UAP (n=44)
Non-ACS (n=76)

Fig. 1. Inclusion and exclusion criteria.
ACS = acute coronary syndrome; ECG = electrocardiogram; UAP = unstable angina pectoris; STEMI = ST-segment elevation myocardial infarction; NSTEMII = non-STEMI.

Mean QTD of patients with ACS was significantly greater than that of patients without ACS (39.61±12.9 vs. 32.56±15.1, p=0.004). Similarly, mean QTcD of patients with ACS was significantly greater than that of non-ACS patients (46.12±16.3 versus 38.10±18.2, p=0.009). An ROC curve was created, to determine the diagnostic value for ACS of the QTD and QTcD of the initial ECGs (Fig. 2), and the AUC was calculated. AUC was 0.624, p=0.015 for QTD, and 0.603 and p=0.049 for QTcD. When various cut-off points were evaluated, potentially useful values for predicting ACS

TABLE
Patient Characteristics and Final Diagnosis

	ACS (n=51)	Non-ACS (n=86)	p value
Patient Characteristics			
Gender (Female/Male) (n)	20/31	36/50	0.901
Age (mean±SD)	61.61 ±11.8	46.49 ± 14.8	<0.001
Duration of pain / minute (median, IQR)	120, IQR 180	60, IQR 101	<0.001
History of myocardial infarction (n, %)	14 (%27.5)	12 (%14)	0.085
Outcome Measures			
QT dispersion (ms)	39.61±12.9	32.56±15.1	0.004
QTc dispersion (ms)	46.12±16.3	38.10±18.2	0.009

SD=standard deviation, IQR=interquartile range.

were between 30 and 50 ms for QTD (sensitivity 86% and 10%, specificity 35% and 97%, respectively). These values were 40.5 and 49.5 ms for QTcD (sensitivity was 96% and 32%, specificity was 12% and 77%, respectively).

Discussion

One study found that in 30–40% of the admissions with chest discomfort, the diagnosis was ACS (14). It is very important to evaluate patients with chest pain and normal initial ECG in ED. The common feature of the ACS group is that morbidity and mortality decrease significantly if the diagnosis is rapid and the therapy is specific. Therefore, in the emergency setting, it is critical to make appropriate decisions on whether to admit or discharge patients with chest pain of ischemic cause and nondiagnostic ECGs. For these patients, diagnostic cardiac indicators in the serum need time to reach a significant level, and waiting for the results leads to the loss of the crucial period known as the golden hour. In this study, we found that for patients with chest pain and nondiagnostic ECGs who were admitted to the ED, the QTD and QTcD means were different for the ACS and the non-ACS patients. The QTD and QTcD values that were found to be useful in ACS diagnosis, were 40 ms.

Manual QTD measurement is criticized as being operator-dependent (15). It has been reported that automatic and manual QTD measurements differ, but in good-quality ECGs, the difference between the normal and abnormal groups can be determined (16). We excluded the unclear ECG determinations, to decrease the problem. Generally manual paper speed is 50 mm/s but in ED this is 25 mm/s. In order to make a rapid and practical evaluation of the initial ECG, we calculated the QTD and QTcD with a 25 mm/s speed, as recommended by Calder et al. (1).

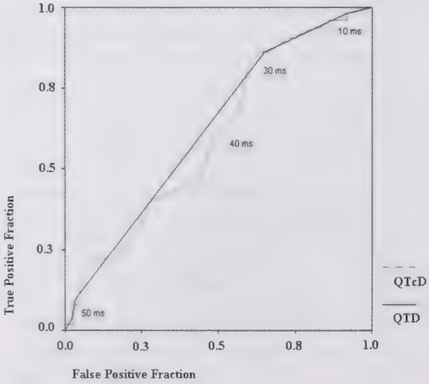

Fig. 2. Receiver operating characteristic curve for QT dispersion and QTc dispersion.
QTD = QT dispersion, QTcD = QTc dispersion.

Both animal and patient data have shown that during ischemia, repolarization time in the hypoperfused areas tends to shorten. In contrast, infarcted areas are associated with prolonged recovery times, which may result in increased dispersion of repolarization compared with the baseline state (17). Many studies have shown that QTD appears with coronary ischemia. The presence of QTD is also an indicator of myocardial electrical instability and increased arrhythmic mortality. In addition, QTD increase is seen as a response to temporary myocardial ischemia during an exercise test and there is a significant correlation between the QTD and degree of ischemia (18). In a study by Suzuki et al. (8) comparing atypical chest pain and vasospastic angina patients, it was found that QTcD is significantly longer for the vasospastic angina group and that QTD decreases after isosorbide dinitrate application in this group. When compared with healthy controls, QTD was longer in UAP patients and also in survivors when compared with the patients who died during follow-up (19). Independent of severity and localization of coronary artery disease, QTD is seen in myocardial ischemia (20). One study reports that combining automatic QTD measurement with other diagnostic methods has a potential clinical role in identifying AMI and acute cardiac ischemia (21). In this study we found that QTD and QTcD values are higher for ACS patients than for patients without ACS.

For patients who were admitted to the ED with chest pain and nondiagnostic initial ECG but later diagnosed as having AMI, QTD was longer than for the healthy controls, and found to be 44.6 ms (11). It has been suggested that initial QTD level has a low predictive power for new cardiac events, but that QTD can be more helpful for low-risk patient group, and that there is a significant correlation between QTD and mortality. The median QTD value has been determined to be 40 ms (15). As with earlier reports, the present study showed that if QTD and QTcD are over 40 ms, development of ACS is very probable despite the normal initial ECG.

The present study showed that the QT dispersion was greater for those patients who had a final diagnosis of ACS. However, QT dispersion appears to have poor ROC (0.624 or 0.603 for QT and QTc, respectively). This makes the test only slightly better than chance and not particularly valuable as a diagnostic test in the routine clinical setting.

Conclusion

The present study demonstrated that QTD and QTcD means were markedly greater for patients who had a final diagnosis of ACS. The QTD and QTcD values that were found to be useful in predicting the likelihood of ACS were both 40 ms. However, difficulty with operator measurements of QT dispersion would limit its value as a diagnostic test.

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Surgical Treatment of Skier's Thumb Injuries:

Case Report and Review of the Literature

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Abstract

Inappropriate treatment of skier's thumb injuries has been reported to result in chronic painful instability, weakness of pinch, and arthritis. Therefore, surgical treatment is recommended for those fractures with 2 mm or more of displacement, or significant articular involvement with incongruency or rotation. The goal of surgery is restoration of anatomy with stable fixation.

In this study we present some cases managed with internal fixation of the injury. This technique has the advantage of anatomic stable fixation with good outcome.

Key Words: Thumb, fracture, open reduction, internal fixation.

Introduction

"GAMEKEEPER'S THUMB" was the term coined in 1955 to describe the chronic injury to ligaments of the thumb, seen in gamekeepers in Scotland who killed wounded rabbits by grasping and twisting the animal's neck between the base of the thumb and index finger (1). The injury involves the ulnar collateral ligament (UCL) of the metacarpophalangeal (MCP) joint of the thumb. Although caused by long-term stress, gamekeeper's thumb is virtually identical to the now more common acute injury called "skier's thumb." Skier's thumb results from the forceful adduction of a skier's thumb when it is rammed against the ski pole during a fall or other mishap. Impact with a steering wheel in an auto collision is another common cause of this injury (1).

In 1962 Stener was the first to describe the displacement of the completely ruptured UCL proximal to the aponeurosis of the adductor pollicis muscle (2). In Stener's lesion, the displaced ligament cannot fall back spontaneously to its original position, and operative treatment is necessary to prevent chronic joint instability and subsequent arthritic changes (2, 3). The UCL is either avulsed from its insertion on the base of the proximal phalanx with or without a bone fragment or torn in its substance with the distal torn end deep to the adductor aponeurosis (3). An unrecognized Stener lesion usually causes chronic laxity of the UCL. For this reason a conclusive diagnosis of the pathologic features of the UCL is crucial for determining treatment (3).

Evaluating UCL injuries of the MCP joint of the thumb is difficult and relies on good clinical assessment and experience (4). Traditionally, diagnosis has been obtained by clinical examination supported by conventional radiography, arthrography, magnetic resonance imaging (MRI), and ultrasound studies (5, 6). There is some debate in the literature about absolute guidelines for the clinical assessment of incompetence of the UCL. Probably the most accurate parameters were proposed by Heyman et al., who suggested 35° of laxity of the

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ulnar side of the MCP joint when stressed in extension and 15° more laxity than the contralateral side when stressed in 30° of flexion (7).

Several authors have reported good results with ultrasonographic examination of the integrity of the UCL in skier's thumb, although substantial experience of the examiner and proper hardware to distinguish the soft tissue structures seen during examination are crucial (6, 8, 9). Ultrasound and magnetic resonance imaging have been used to evaluate ligamentous injuries, but are not indicated for skier's thumb injuries (9, 10).

Inappropriate treatment of skier's thumb injuries has been reported to result in chronic painful instability, weakness of pinch, and arthritis (11, 12). Therefore, surgical treatment is recommended for those fractures with 2 mm or more of displacement, or significant articular involvement with incongruency or rotation. The goal of surgery is restoration of anatomy with stable fixation. The aim of this study was to evaluate the results of surgical treatment of skier's thumb injuries.

Patients and Methods

This is a retrospective review of 16 patients with 16 skier's thumb injuries fixated with screws or Kirschner wires, between March 1993 and August 2003. Information was obtained through review of clinic notes, photographs, hand therapy measurements, and operative reports.

The group consisted of 14 men and 2 women with an average age of 35.5 years (range, 18–68). The dominant hand was involved in 14 cases. Mechanism of injury included falls from a standing height (n = 4), sports injuries (n = 6), blunt crush injuries (n = 4), and a motor vehicle accident (n = 2). The diagnosis was confirmed after physical examination and standard radiographs. During this period all skier's thumb injuries were treated operatively. The average time from trauma to operation was 12 hours (range, 4–48).

All of the surgeries were performed using regional anesthesia. A chevron-shaped incision with the apex volar to the mid-axial line of the MCP joint was used. This incision allows for adequate exposure volarly where the fracture is located, and dorsally where a sensory nerve to the thumb must be identified and protected. The joint and fracture site were inspected and cleared of hematoma. The choice of fracture fixation technique depends on several factors, including the size of the fragment, the presence of comminution, and the experience and preference of the surgeon. Screw fixation (1.0 mm or 1.5 mm) was used in 14 patients and Kirschner wire fixation was used in the remaining two.

The initial splint was removed within one week of surgery, a forearm-based thumb spica splint was fabricated, and flexion and extension exercises were given. X-rays were checked every 3 weeks until the fracture healed. Immobilization was continued for 6 weeks. At 6 weeks after surgery, the fractures were healed, strengthening exercises were begun, and splinting was discontinued.

Bony union was confirmed by review of the radiographs. Range of motion of the thumb was measured with the use of a standard goniometer. Results were considered excellent, good, fair or poor according to criteria defined by Gingrass (Table).

Case Report

One of the patients, a 42-year-old man, had a trauma to his right thumb after falling from a height, resulting in a skier's thumb injury (Fig. 1). After radiographic examination Kirschner wires were used to fixate the fracture (Fig. 2). After 3 months the wires were removed because of skin irritation.

Results

The final evaluation was performed by the first author (MD), with the evaluation protocol consisting of standard radiographs of the hand and functional assessment of thumb. The average follow-up period was 4.5 years (range, 2–10).

All of the fractures had united by 6 weeks, with a mean of 4 weeks (range, 3–6). Union was

TABLE

Gingrass' Criteria for Assessment of Thumb Injuries

Palmar Abduction	Excellent	Good	Fair	Poor
>45°	TF > 100°	TF 60–100°	TF 0–60°	
40–45°		TF >75°.		
30–40°			TF >80°	
<30°				TF <80°

TF = total flexion of metacarpophalangeal and interphalangeal joints.
Result is lowered one category if interphalangeal flexion <10°.

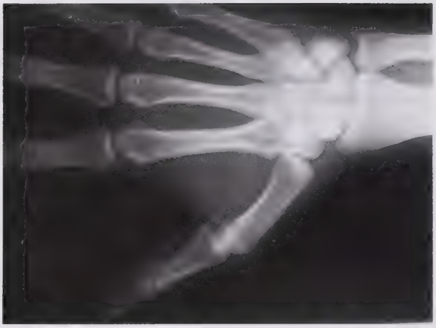

Fig. 1. Preoperative X-ray of case.

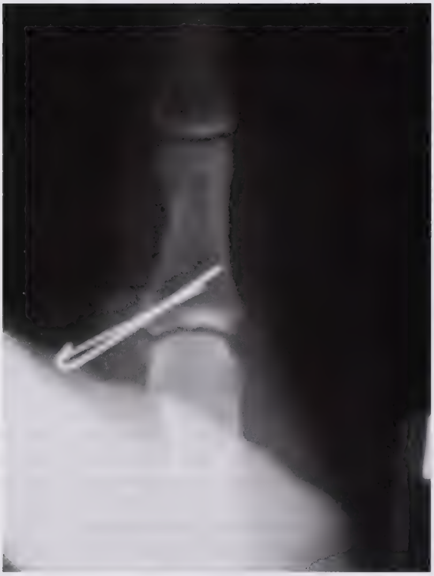

Fig. 2. Fixation of skier's thumb with Kirschner wires.

defined radiographically and clinically with physical examination. To assess function of the thumb, Gingrass criteria were used (Table). According to these criteria, 13 patients had excellent results and 3 patients had good results.

Complications included superficial infection and hardware removal in 2 patients who had a fixation with Kirschner wires. The superficial infections resolved with oral antibiotics and local wound care. In addition, both of these patients required a second surgical procedure for hardware removal because of prominence and skin irritation at 12 and 22 weeks, respectively. We identified no cases of deep infection, and no patient required wound coverage because of a skin complication. We did not identify any patients with nonunion, malunion, complex regional pain syndrome, tendon rupture or neurological problem.

Discussion

The aim of this study was to evaluate the results of surgical treatment of skier's thumb.

Inappropriate treatment of these injuries has been reported to result in chronic painful instability, weakness of pinch, and arthritis (11, 12). Therefore, surgical treatment is recommended for those fractures with 2 mm or more of displacement, or significant articular involvement with incongruency or rotation. The goal of surgery is restoration of anatomy with stable fixation.

The choice of fracture fixation method depends on the size of the fracture fragment as well as surgeon experience and preference. For larger fractures, it is preferable to use 1.5 mm minifragment screws with interfragmentary compression (12). Tension band wiring or Kirschner wire fixation is a useful technique for those fragments not large enough to support a screw, whereas the use of suture anchors is recommended for smaller and comminuted fractures (11, 12).

It is important to note that the ulnar collateral ligament must be reattached, reconstructed, or reconfigured as close as possible to its original configuration. Failure to do so may alter normal MCP joint range of motion (13). Bean et al., in an *in vitro* study, repositioned the proximal origin of the UCL, in sequence, 2 mm palmar and 2 mm proximal from its original anatomic location. They noted that palmar placement of the origin of the UCL increased radial deviation from a mean of 18 to a mean of 27 degrees; proximal placement decreased it from 18 to a mean of 11 degrees. There was no effect on flexion or extension from displacing the proximal origins of the UCL. The distal insertion of the UCL was detached and repositioned in sequence 2 mm dorsal, 2 mm distal, and 2 mm palmar. Dorsal displacement of the UCL insertion on the proximal phalanx increased radial deviation from 18 to 25 degrees, and distal positioning of the insertion decreased it from 18 to 10 degrees. Distal repositioning of the insertion of the UCL decreased MCP joint flexion from 56 to 47 degrees, and palmar placement decreased it from 56 to 49 degrees. Dorsal displacement had no effect on flexion, and extension and ulnar deviation were not affected by ligament repositioning.

Conclusion

In order to prevent the complication of nonoperative treatment of skier's thumb injury, surgical fixation is recommended.

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Isolated Metachronous Contralateral Adrenal Metastasis from Renal Cell Carcinoma

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Abstract

Isolated contralateral adrenal metastasis from renal carcinoma is extremely rare. Patients who present with this entity often undergo surgery with the presumed diagnosis of an incidentaloma. A mass in the contralateral adrenal diagnosed following radical nephrectomy for renal carcinoma should be viewed with a high index of suspicion for the presence of metastatic disease. Surgery is the only effective management option and should be offered to these patients.

Key Words: Adrenal, incidentaloma, mass, renal carcinoma, metastasis, adrenalectomy.

Introduction

ALTHOUGH RENAL CELL CARCINOMA (RCC) frequently presents with distant metastases, involvement of the contralateral adrenal gland in the form of an isolated metastasis is rare. We present a patient with a solitary, metachronous metastasis to the contralateral adrenal gland. The relevant literature is briefly reviewed.

Case Report

A 73-year-old woman presented with gross hematuria and flank pain. Diagnostic evaluation, including abdominal computed tomography (CT), revealed a left renal tumor. Bone scan and CT of the chest were negative for metastatic disease. At this time, abdominal CT was without pathologic findings from the right adrenal. Left radical nephrectomy was performed with en bloc resection of the left adrenal gland. Pathologic examination revealed renal cell carcinoma without regional lymphatic metastases. Abdominal CT, performed 6 months later for routine re-evaluation of the patient (follow-up) showed a homogeneous enlargement of the right adrenal gland (d=5 cm), with regular, smooth margins, and without invasion of the adjacent anatomic structures. Due to the marginal diameter of this lesion, 3 months later, we recommended that a repeat abdominal CT be done. This showed an increase in the size of the right adrenal gland (d=5.5 cm), again with the same characteristics (Fig. 1). Laboratory investigation showed that this adrenal mass was not associated with any endocrine activity. Due to the previous history of RCC, computed tomography of the head and the thorax was performed to exclude metastatic disease before surgery. The results were negative. The patient underwent surgery with the presumed diagnosis of an adrenal neoplasm ("incidentaloma"). A right adrenalectomy was performed through an extended right Kocher incision. At surgery, the right adrenal gland was enlarged, but without invading adjacent structures. The postoperative course was uneventful and the patient was discharged on postoperative day 5. Pathologic evaluation (including immunohistochemistry) showed the presence of adrenal metastasis from the previous RCC (Fig. 2). The patient was doing well 6 months after surgery.

Discussion

Adrenal glands represent a usual site of metastasis for tumors of several solid organs, including lung, stomach, esophagus, liver, kidney, and breast

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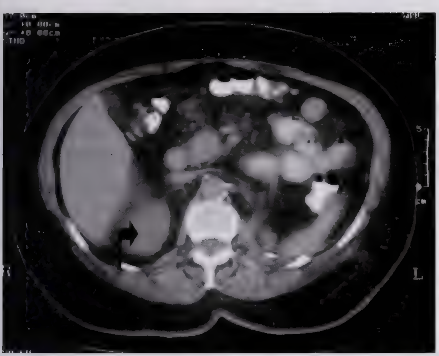

Fig. 1. The right adrenal mass (curved arrow), with smooth regular margins and without invasion of the adjacent anatomic structures.

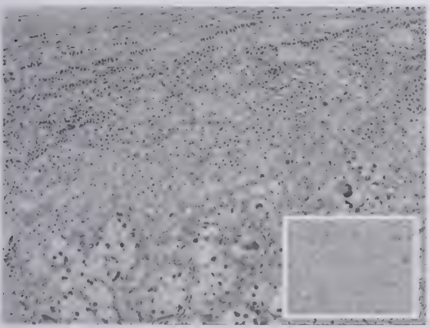

Fig. 2. Histological section from the right adrenalectomy specimen showing metastatic deposits of RCC (conventional clear cell type). Carcinoma cells show irregular nuclei and prominent nucleoli. A rim of normal adrenal tissue is identified (Hematoxylin-eosin stain, magnification × 100). Inset: Histological section from the left nephrectomy specimen, showing RCC.

(1). Even though RCC has the ability to invade almost all organs, and by the time of diagnosis the tumor has already spread in 20–30 % of patients (2), adrenal involvement is not very common. During autopsy of patients who had generalized RCC, metastasis to the ipsilateral adrenal was found in 7–23% of patients (3, 4), whereas involvement of the contralateral adrenal was observed in only 11% (5, 6). Solitary metastasis of RCC to the ipsilateral adrenal was observed in only 3% and to the contralateral one in less than 1% (7–10). Therefore, isolated, contralateral adrenal metastasis of RCC is extremely rare. Most commonly, solitary contralateral adrenal metastases are synchronous tumors diagnosed during the initial evaluation and staging of primary renal tumor. Less often, these are metachronous lesions, and diagnosis is made during routine follow-up of patients having already been treated by radical nephrectomy. The time from primary treatment to metastasis varies (up to 23 years) (9). Dieckmann et al. (6) reported a mean time of 5.3 years after nephrectomy, whereas Lau et al. (1) reported 6.2 years. The spreading pathway that may explain the appearance of this solitary metastasis to the contralateral adrenal remains unclear. A possible explanation could be that adrenal cells show an endogenous "predisposition" for invasion from metastatic renal carcinoma cells (4, 11, 12).

Diagnosis of metachronous contralateral adrenal metastasis occurs during regular follow-up, most frequently by using abdominal ultrasonography and/or abdominal CT. CT scan is the diagnostic method of choice for the evaluation of these patients. MRI has no advantages over CT (10).

Given that conservative treatment, such as chemotherapy, hormonal therapy and radiotherapy, has not proved to be effective in metastatic RCC, surgical removal of solitary adrenal metastasis remains the only treatment option for these patients. Only surgical treatment can achieve satisfactory survival rates; however, it is difficult to estimate overall survival due to the small number of such cases. Some authors have reported that adrenalectomy can achieve a 5-year survival of about 60% of patients with contralateral adrenal metastasis from RCC (11). Kessler et al. (7) reported a relationship between survival and the time from nephrectomy to diagnosis of metastasis. They set a cut-off limit of 18 months from primary treatment, beyond which patients show better survival rates. According to these authors, the longer the interval between nephrectomy and the appearance of the adrenal metastasis, the better the prognosis. Probably this latency in the appearance of metastasis represents a less aggressive behavior of cancerous cells, with slower progression that connotes a better prognosis.

In general, adrenal masses represent non-functioning benign tumors. These are often incidentally discovered ("incidentalomas") during diagnostic evaluation of patients for other, unrelated complaints or indications. These tumors are most commonly asymptomatic and without any clinical significance when their diameter is < 5 cm. However, the risk of underlying malignancy increases if the diameter of the lesion exceeds 5 cm. Expectant management (follow-up) is therefore indicated for lesions < 5 cm. However, if the lesion is > 5 cm or if its size increases, surgery is indicated. In the presence of a history of a malignant disease, and in particular RCC, every adrenal mass should be viewed with a high index of suspicion for the presence of metastatic disease, even if the mass has been diagnosed many years following nephrectomy. These metastatic lesions are not easily distinguished from primary non-functioning adrenal tumors. Adrenalectomy is indicated for these patients, since there is no other effective treatment of metastatic disease from RCC (6). Although the discovery of an adrenal metastasis in patients with RCC automatically means that they have advanced stage disease, adrenalectomy can occasionally achieve long-term survival for them (1, 7, 13). The role of adjuvant therapy is limited in the management of these patients, since chemotherapy is ineffective in RCC (14). Immunotherapy may be used as adjuvant therapy, but it should be used as an investigational method in the frame of a research protocol.

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Intestinal Perforation due to Miliary Tuberculosis in a Patient with Behçet's Disease

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Abstract

Gastrointestinal manifestations of both Behçet's disease and intestinal tuberculosis include the signs and symptoms of abdominal pain, weight loss, fever, vomiting, diarrhea and palpable mass in the right lower quadrant.

We report the case of a male patient with Behçet's disease who had multiple ileal perforations due to miliary tuberculosis. It was suspected that the perforations were due to intestinal manifestation of Behçet's disease, but the final pathology report and chest X-ray one week after surgery demonstrated the presence of miliary tuberculosis. To our knowledge, this is the first reported case of Behçet's disease with intestinal perforation due to miliary tuberculosis.

Key Words: Behçet's disease, intestinal perforation, miliary tuberculosis.

Introduction

BEHÇET'S DISEASE (BD) is a type of systemic vasculitis characterized by recurrent oral and genital ulceration and ocular inflammation. Since its original description, the additional involvement of many other organs, including joints, skin, blood vessels, nervous system, and gastrointestinal tract, has been reported (1).

Since the etiology of BD remains unknown, its treatment is usually symptomatic and palliative. Patients are usually treated with antibiotic, antiviral, corticosteroid and immunosuppressive agents according to the symptoms (2, 3). Immunosuppressive and cytotoxic agents are used for more severe involvement (3), but this causes patients to be more susceptible to opportunistic infections.

We describe a patient with Behçet's disease who presented with military tuberculosis, which most probably developed secondary to steroid use.

Case

A 34-year-old man was admitted to our hospital complaining of acute abdominal pain, fever, dyspnea and poor appetite. Physical examination revealed abdominal tenderness and rebound. Chest X-ray showed normal lungs and free air under the right diaphragm (Fig. 1). The patient had been on corticosteroid treatment for BD for 5 years, in doses ranging from 5 to 40 mg. He was given colchicine for 1 year and discontinued 2 years ago. On rare occasions, he used naproxen for his joint pains. He did not report use of aspirin.

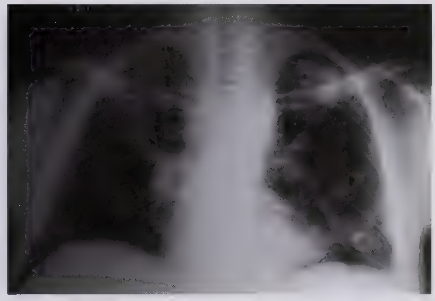

Fig. 1. Free air under the right diaphragm.

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The patient, who was operated on, had been diagnosed as having intestinal perforation due to BD. During the exploratory laparotomy, three separate perforations, in a 35 cm segment of small bowel and 40 cm proximal to the caecum, were observed (Fig. 2). The involved segment was resected and an ileoileostomy was performed. After the operation, the patient was taken to the intensive care unit. His first three postoperative days were uneventful; however, a fecal fistula developed on the fourth postoperative day. The patient was taken to the OR. During the exploratory laparotomy, a few intestinal collections around the anastomosis and a 1 cm anastomotic dehiscence were found. We did an abdominal "washout" and the anastomosis was converted to an end ileostomy. An X-ray of the chest, taken on postoperative day five, showed multinodular infiltration in both lungs. The patient died on the seventh postoperative day, due to sepsis. Microscopic examination of the specimen revealed mucosal ulceration and necrotizing granulomas in the submucosal stroma and muscularis, as well as in the Payer's patches (Fig. 3). Acid-fast bacilli were present in the area of the caseating granuloma.

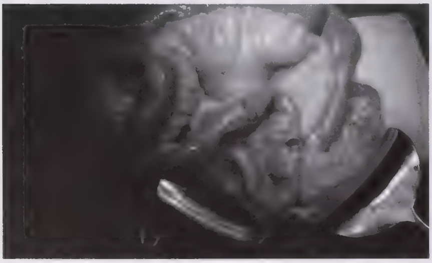

Fig. 2. Three separate perforations at the terminal ileum.

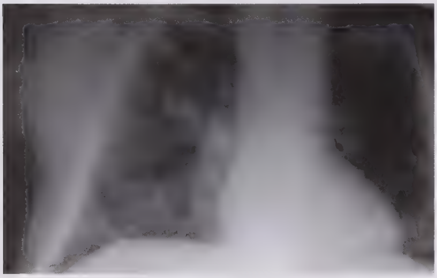

Fig. 3. Multinodular infiltration in both lungs.

Discussion

Tuberculosis of the gastrointestinal tract is usually secondary to pulmonary infection. A rare cause of gastrointestinal tuberculosis is bowel involvement during miliary tuberculosis by hematogenous spread (4, 5).

Pulmonary tuberculosis may rarely occur in patients with BD and is an important differential diagnosis, although less common than the pulmonary disease due to underlying vasculitis that is seen in BD (6, 7). There are a number of possible factors that may increase the risk of tuberculosis in patients with BD: the disease itself may produce a defect in cell-mediated immunity, which increases the individual's susceptibility to tuberculosis (6); the immunosuppressive drugs, particularly corticosteroids, used in BD, predispose these patients to developing tuberculosis (8). A common genetic background, HLA-B5, to both diseases is well known (9).

Gastrointestinal manifestations of both BD and intestinal tuberculosis have similar clinical and histological findings, and they usually affect the same segment of the intestine. The most common signs and symptoms of these two diseases are abdominal pain, weight loss, fever, fatigue, loss of appetite, vomiting, diarrhea and palpable mass in the right lower quadrant (10, 11).

The typical internal manifestation of both diseases is round or oval ulcers that can be seen throughout the alimentary tract, but most commonly in the terminal ileum and the caecum (12, 13).

Intestinal perforation due to military tuberculosis is extremely rare and only two cases have been reported (10, 11). Although any part of the intestine may perforate, the most frequent site is the distal ileum. A single perforation is present in 90% of cases. Multiple perforations are uncommon (14, 15). Free perforation is uncommon in intestinal tuberculosis due to reactive thickening of the peritoneum and the formation of adhesions to adjacent tissues (16).

Morbidity and mortality of the two diseases are high. The overall mortality rate of perforation ranges from 30–67%, even when there has been surgical treatment. The mortality is higher for patients who have had two or more perforations (14, 17, 18).

Surgical treatment of these lesions varies from simple drainage of peritoneal or pelvic abscesses to resection of the involved bowel. The most effective treatment is resection of the diseased segment with an end-to-end anastomosis, but the final decision depends upon the general condition of the patient, extent of the disease and presence or absence of strictures distal to the perforation (19).

Toxemia, wound dehiscence, adhesive obstruction and fecal fistula have been usual complications in both diseases (19).

Although intestinal perforation due to both BD and military tuberculosis is uncommon, in this patient, tuberculous perforation, perhaps due to a predisposition after steroid use, was observed.

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Book Reviews

Cancer and Its Management.

Robert Souhami and Jeffrey Tobias.
5th edition. Malden, MA:
Blackwell Publishing; 2005.
533 pp. $69.95.
ISBN-13: 978-1-4051-26366;
ISBN-10: 1-4051-26361.

Cancer and Its Management, by Robert Souhami and Jeffrey Tobias, states in the preface that it is an introductory text for doctors, nurses and other medical professionals, as well as for students and scientists interested in the problem of cancer. They say that this book is not for specialists in cancer medicine, but rather for general practitioners and trainees in medicine, surgery and gynecology. This is the book's fifth edition, with the first edition having been published in 1986, and it is apparently authored entirely by these two physicians. Reading through this book, one realizes how fortunate we are to have seen so many rapid advances in recent years, but this book unfortunately does not keep up with these advances.

In the chapter on breast cancer, on page 227, the authors state that the current sequence of therapy should be local surgical excision plus axillary dissection; combination chemotherapy; and finally, radiation therapy—a dramatic change even from ten years ago. Patients should also receive tamoxifen if they are ER-positive. Even though sentinel node biopsy is mentioned previously in the chapter, in this statement it is forgotten that axillary dissection, which is no longer performed in this country before sentinel node biopsy, is no longer the standard. The ATAC trial demonstrating the superiority of an aromatase inhibitor is previously mentioned, but here the authors still mention only tamoxifen. The discussion on adjuvant chemotherapy is quite up to date, even mentioning the use of dose-dense chemotherapy programs and their superiority over conventional treatment. One thus wonders why the discussion of hormonal therapy is not equally up to date.

Again, in the discussion of metastatic disease, tamoxifen is listed as initial therapy and the aromatase inhibitors are recommended as second-line therapy after tamoxifen. The question of bone marrow transplantation seems to be unresolved for these authors, even though it has been discredited by most specialists in the field, and there is no mention of Xeloda (capecitabine), Navelbine (vinorelbine) and Gemzar (gemcitabine), excellent agents used either alone or in combination in metastatic regimens, or together with Herceptin.

The chapter on genitourinary cancer does not mention the recent advances in partial nephrectomies or the dramatic successes with targeted therapy using sorafenib, sunitinib, and Avastin (bevacizumab). In the section on lung cancer, there is no discussion on the recent acceptance of adjuvant chemotherapy for almost all stages of lung cancer, and there is also no discussion of combined radiation and chemotherapy in Stage IIIA. Gefitinib is mentioned for its use in adenocarcinoma; however, its real efficacy is in bronchoalveolar cancer, a subset of adenocarcinoma, and this should have been mentioned. In discussing chemotherapy in non-small-cell lung cancer, the authors state that this is still a matter of clinical judgment, whereas most oncologists today believe there is definite benefit, and unless there is comorbidity, in this country most people do undergo chemotherapy. Their chart is rather puzzling in that they list single agents separately and then combination therapy for advanced disease, but there is no mention of carboplatin, an often-employed agent in either single agent therapy or combination therapy. Paclitaxol, docetaxel, vinorelbine, and gemcitabine are not even mentioned in connection with combination therapy, even though they are all used in combination chemotherapy with excellent results. And there is no discussion of video-assisted thoracoscopy in the discussion on surgery.

In the chapter on colon cancer, the authors do mention attempts at controlling metastasis with partial hepatectomy, but omit the fact that patients with metastatic disease to the liver are now considered curable with aggressive chemotherapy following removal of their lesions. In the discussion on adjuvant chemotherapy, the authors state that there is increasing evidence that this may be valuable. This is a considerable understatement; for example, they fail to mention the positive results with the MOSIAC Trial combining oxaliplatin, 5-

fluorouracil, and leucovorin. Finally, capecitabine is not mentioned, and this drug has shown results equal to or better than those of 5-fluorouracil in metastatic diseases and may replace infusional 5-fluorouracil in adjuvant trials.

The brief comments on living with a colostomy are excellent not only for medical students and general practitioners, but for specialists as well. It imparts excellent advice to physicians concerning the problems faced by these unfortunate patients. Finally, in the chapter on pancreatic carcinoma, gemcitabine, the standard drug, with about a 15% response rate, is not even mentioned.

The chapter on Hodgkin's disease and non-Hodgkin's lymphoma is much better organized than (for example) the lung cancer chapter, because there is a discussion of each stage of the disease and its treatment, thus making it easier for the reader to follow. Yet there is no mention of PET scanning for staging in both the Hodgkin's/non-Hodgkin's lymphoma and lung cancer chapters, even though PET scanning is mentioned in the chapter on radiology. PET scans do add greatly to staging in these diseases and should have been mentioned in these chapters.

The idea of writing a textbook on cancer management for nonspecialists is a good one. Unfortunately, this particular text is already outdated at the time of its publication.

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Ascites and Renal Dysfunction in Liver Disease: Pathogenesis, Diagnosis and Treatment.

Pere Gines, Vicente Arroyo,
Juan Rodes, and Robert W. Schrier,
editors. 2nd edition. Malden, MA:
Blackwell Publishing Ltd.; 2005.
450 pp. $174.94.
ISBN-13: 978-1-4051-1804-0;
ISBN-10: 1-4051-1804-0.

Ascites and Renal Dysfunction in Liver Disease, published in 2005, is the second edition of the original book first published in 1999. An ominous development in the progression of liver disease is the onset of renal dysfunction in the patient with ascites. The current organ allocation system in the United States reflects the key prognostic value of serum creatinine, incorporating it into the model for end-stage liver disease. One of the most difficult challenges for clinicians caring for patients with advanced liver disease is management of portal hypertension with concomitant renal insufficiency. Thus any physician involved in managing cirrhotic patients needs to be familiar with the pathogenesis and differential diagnosis of renal dysfunction in this setting. A number of seminal studies appearing in recent years have had a profound impact on our understanding and sophistication in the management of ascites with and without renal insufficiency. Many of these studies were conceived by the editors of this textbook, who are based in Barcelona and Colorado.

The contributors provide lucid discussions of the pathogenesis of the fluid retention leading to ascites and explore mechanisms, including hemodynamic abnormalities, that culminate in the manifestations of decompensated cirrhosis. Each of the chapters devoted to basic mechanisms is linked to other chapters describing clinical manifestations and therapy.

This book is an excellent resource for physicians, especially hepatologists and nephrologists treating complications of cirrhosis, with its elaborate and exhaustive description of the pathophysiology underlying renal dysfunction in cirrhosis. The content and level of writing in this book are superb. The writing flows well and is enjoyable to read. Particularly useful are the chapters that address renal involvement in liver disease in the absence of cirrhosis, as in acute liver failure, obstructive jaundice and viral hepatitis. The use of TIPS in refractory ascites and especially of vasoconstrictors in hepatorenal syndrome are relatively new concepts in this field and are well covered. The book should be on the office shelves of clinicians who see many patients with advanced liver disease.

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Practical Transfusion Medicine.

Michael F. Murphy and
Derwood H. Pamphilon, editors.
2nd edition. National Blood Service,
John Radcliffe Hospital, Oxford and
Bristol Center, Bristol (UK):
Blackwell Publishing Ltd.; 2005.
469 pp. $115.00.
ISBN 1-4051-1844-X.

Many clinicians require a working knowledge of transfusion medicine to provide state-of-the-art, cost-effective care and to educate patients about their clinical options. *Practical Transfusion Medicine* is a concise, comprehensive but user-friendly guide to transfusion medicine, meeting the needs of a wide variety of clinicians as well as hematologists in training and consultants in established practices. Forty-nine authors, primarily from the U.K., have contributed to the 39 chapters presented in this volume. The book was released in May 2005 in Europe and in July 2005 in the United States. Evaluating this text for a U.S. audience, the reviewer was interested to discover if transfusion practices peculiar to the U.S. would be covered adequately and to learn if authors had been able to incorporate some of the most recent developments in transfusion medicine before going to press.

The chapters are grouped in five sections: (1) *Basic principles of transfusion*; (2) *Clinical transfusion practice*; (3) *Complications of transfusion*; (4) *Practice in blood centers and hospitals*; and (5) *Developments in transfusion medicine*. Despite the large number of contributors, the writing styles of the authors (or the editors' guiding hands) are amazingly congruent, allowing the reader to move from chapter to chapter without having to adjust the pace because of idiosyncrasies of style or grammatical phrasing.

Basic principles of transfusion includes an introduction that provides an overview of blood safety, concerns about best transfusion practices, donor recruitment and retention issues, and patient education about blood transfusion. A review of basic immunology then prepares the reader for subsequent chapters on human blood groups, human leukocyte antigens, and platelet and neutrophil antigens. The chapter on blood group antigens focuses on antibodies commonly encountered in everyday practice. This was a wise decision, as it is impossible for anyone outside a reference laboratory to remember the 285 blood group specificities recognized by the International Society for Blood Transfusion. The chapter on human leukocyte antigens provides an excellent introduction to the HLA system and its role in transfusion and transplantation. The text describes techniques currently being used by most laboratories, but it was disappointing that there were no figures illustrating these techniques. The chapter on platelet and neutrophil antigens effectively employs a combination of text and tables to explain shared antigen systems and neutrophil and platelet-specific antigen systems. Figures illustrating the test systems frequently used to detect anti-platelet antibodies and perform DNA-based typing for platelet-specific antigens are included.

The section on *Clinical transfusion practice* has chapters on effective and safe use of blood components, bleeding associated with trauma, prenatal and childhood transfusions, transfusion in hematological disease and for solid organ transplants, inherited and acquired coagulation disorders, and use of intravenous immune globulin. The chapters are all well written, providing basic information as well as recommendations for patient evaluation and management. The chapter on safe and effective use of blood components provides a clear and concise description of how clinical staff can prevent the most common risks of transfusion, i.e., having a patient receive a blood product intended for someone else, and having a product transfused that does not meet the special requirement the patient's clinical condition demands. The chapter "*Bleeding associated with trauma and surgery*" provides an excellent overview of patient management in the operating room and includes figures as well as text to explain the thromboelastogram.

Complications of transfusion (Part 3) includes chapters on transfusion reactions, immune modulation and graft-versus-host disease, and transfusion-transmitted infections, including a chapter devoted to vCJD. These sections are in general excellent. However, the brief discussion of pre-transfusion testing of platelets for bacterial contamination is not current from the U.S. perspective. The Bac-T/Alert system, which is used to culture platelet samples, is mentioned as an automated system that might be appropriate for screening, but it is already widely implemented. The Pall BDS system, which screens for bacterial contamination by measuring oxygen consumption, is not mentioned. And the Pall Acrodose system, which permits bacterial testing for pooled platelets, was licensed after the book's publication. There are also differences in U.K. and U.S. practices with regard to irradiation of blood products. Although these differences are described in the text, they would be more easily identified if presented in a table.

Practice in blood centers and hospitals addresses donors and blood collection, blood donation testing and the safety of the blood supply, production and storage of components, medico-legal aspects of transfusion, blood transfusion in hospitals, autologous transfusion, tissue banking, cord blood banking, and therapeutic apheresis. Quality systems and quality monitoring are well integrated in this section. Although there are minor differences between U.K. and U.S. practices, the basic principles are the same.

Developments in transfusion medicine includes the expected chapters on blood substitutes, cytokines, stem cell processing and storage, hematopoietic stem cell transplantation, gene therapy, and recombinant antibodies, but also contains chapters on interventional trials in transfusion medicine, and evidence-based transfusion medicine. This section concludes with a chapter on the future of transfusion medicine.

The information on design of interventional trials in transfusion medicine is essential reading for every clinician who has not had the opportunity to plan and participate in a research study. It explains the difficulties associated with conducting clinical trials in transfusion medicine and provides guidance for evaluating the quality of research studies.

Practical Transfusion Medicine is concise, clinically oriented, and user-friendly. It adequately informs but does not overwhelm the reader new to the discipline. Despite small differences in transfusion practice between the U.S. and the U.K., the concise, clear presentation of clinical material is outstanding and would be of value to hematologists and pathologists in training as well as clinicians in many specialties.

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Alexander Richman Commemorative Lecture

Culture, Moral Experience and Medicine

Arthur Kleinman, M.D.[1], and Peter Benson[2]

Abstract

No one can doubt any longer that culture is crucial to medicine. The evidence for health disparities across ethnic and racial groups as well as for cultural influences on health care practices is too impressive to overlook. Yet the concept of culture and how it is employed in medicine today is quite different from the way culture is now regarded in anthropology, the discipline that originated and popularized the concept. Rather than understand culture as a "timeless" ethnic stereotype applied to patients—which is a common but dangerous practice—physicians need to understand how culture influences doctors as much as patients. And physicians need to understand that culture is not only about differences in dress, etiquette and diet, but also and most profoundly, about what really matters to people. That is, culture is about the changing moral experiences of patients, families, and practitioners, and how those moral experiences powerfully affect the doctor-patient relationship. This article suggests that there is a moral crisis in today's medicine that reflects global cultural transitions. This crisis must be addressed if practitioners are to provide care at the highest moral and human level.

Key Words: Culture, moral experience, medicalization, anthropology, doctor-patient relationship.

Introduction

THE ISSUE OF CULTURE has become very important in health care and biomedical circles in the United States. This is not surprising. American society is one of great social, cultural, and ethnic diversity. And yet it also exhibits great health disparities across racial and ethnic groups (1). For all the medical advances of the past century, health disparities have not been eradicated. Rather, they seem to have widened. And the legacy of institutional racism is not absent from health care and biomedicine (2). It is for these reasons that culture matters in the clinic. And medicine exists in a culture. Cultural factors are crucial to diagnosis, treatment, and care. They shape health-related beliefs, behaviors, and values (3, 4). But medicine has not given culture the same degree of critical analytic attention it gives to biologically relevant issues. There is loose thinking about what this term means and how it ought to be used. Medicine has identified culture with the patient; hence, the "Latino patient" is assumed to have a core set of beliefs about illness owing to fixed ethnic traits. By contrast, it is assumed that the doctor has no culture.

We want to reconnect the concept of culture to how it is used in anthropology, the field that originated the culture concept (5–9), and to expand upon certain moral, social, and existential questions that make the concept especially relevant to our times. The publication of *The Illness Narratives* by one of us [AK] in 1988 helped to make culture a necessary part of best practices in biomedicine and clinical training (10). In particular, the "explanatory models" approach advanced in that book has been used routinely in the examination of internists and psychiatrists, in the training of nurses and social workers, and in the leading models of how to care for patients from different ethnic and cultural groups. The approach consists of a series of questions that doctors ask patients: What do you call this problem? What do you believe is its cause? What course do you expect it to take? How serious is it? What do you think this problem does inside your body? What do you most fear about this condition? What do you most fear about the treatment?

---

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This approach was intended to reframe culture as "illness meaning." The models provided a method for clinicians to more effectively communicate with patients and get at what an illness episode means for them. But what was originally intended to open up a conversation is often used as a conversation stopper. Explanatory models are materialized as a specific item (like X-rays or blood pressure). Patients' answers are seen as mechanical responses ushering from a static set of cultural beliefs. It is of course highly appropriate and desirable for clinicians to be sensitive to cultural difference. But what culture means in medicine is out of step with what it means in anthropology.

Culture is not seen as homogenous or static by anthropologists, who emphasize that culture is a *process* through which ordinary activities and conditions take on emotional tone and moral meaning for participants. The development of interpersonal attachments, the serious performance of religious practices, the cultivation of an identity, and the embodiment of meaning in physiological reactions—these are all cultural processes. Something crucial is lost when explanatory models are used as a mere checklist. Illness is lived in a social world where sufferers have something at stake. Illness is everywhere a profoundly *moral* experience, since sufferers have things of great personal and collective value to gain or lose. Illness alters life plans and projects. And it provokes a response, however difficult and tenuous. Illness matters because real things are on the line: self-identity, physical and mental health, life chances, social status, employment, finances, religious aspirations, or personal relationships. Seen this way, illness and treatment are embedded in the local moral experience of a particular network, neighborhood, or community. Instead of a checklist, what clinicians want to get at in the explanatory models is what really matters for patients, their families, and for the clinician as well: a combination of cultural and personal meaning.

Culture as Moral Experience

The phrase "moral experience" can be ambiguous, because the word "moral" has several meanings. In its broadest sense, "moral" refers to values. Experience is moral because something matters, is imbued with value. This does not mean that experience is "good" or "bad," which it may be. We are not talking about ethics—what is right to do—but rather about the moral core of experience, the fact that something is at stake for ordinary people, often deeply so. And what matters could be far from what is ethical. Hence, what matters is not universal, but differs across local worlds. Patients have different things at stake, even within ethnic, racial, or cultural sub-groups, because their worlds are distinctive and so are they as individuals. Serious attention to culture should prevent racial profiling or ethnic stereotyping.

The concept of moral experience also makes illness part of a broad category of personal and collective dangers and catastrophes. Life thrusts people into vexing circumstances and confounding conditions. Troubling realities riddle life: divorce, death of a loved one, injustice and discrimination, dead-end jobs, awful relations with supervisors, unemployment, bankruptcy, severe accidents, disability, political oppression, and alienation from one's faith community. And there are large-scale social catastrophes. The Asian tsunami and Hurricane Katrina revealed the limits of prediction and prevention when it comes to natural disasters. They also revealed that government and humanitarian response could compound the problems. Public response was massive, but it was incomplete, confused and sometimes counterproductive. Failed and failing states in Africa, political crises in the Middle East, and countless economic and cultural changes have made people's worlds seem fragile, as have September 11th, the war on terrorism, terrorist bombings in Madrid and London, and the forced evacuation of millions in the American Gulf region.

Illness is a catastrophe too, although a very intimate and bodily one. Illness is much more than a biological condition, then. Illness is principally something that happens *to someone* and *at a certain life juncture*. It singles a person out, and this is why support and recovery networks are so vital. Illness carries economic, familial, occupational, and personal peril. Most people will face the pain and constraint of a chronic condition. They will face diabetes, arthritis, ulcers, heart disease, one or more varieties of cancer, asthma, lupus, or Alzheimer's.

Something crucial is lost when the lived experience of catastrophe is made into a medical pathology, when widely shared feelings of fear, anxiety, and peril are recast as individual abnormality. An epidemiological study conducted four months after September 11, found increased rates of cigarette use among adult smokers in New York City. Increased smoking was associated with probable post-traumatic stress disorder and depression (11). So, cigarette smoking was made into an abnormal response. It was not seen as an ordinary, normal response to the shared experience of danger and uncertainty. Not everyone took up smoking or started smoking more, but those who did probably did not do so on account of individual abnormalities. The feeling that life is changing and threatened—promoted and compounded by media images of September 11th—was a very normal response that gave rise, among other things, to increased smoking rates in New York City.

In response to real dangers and uncertainties, fear, dread, and anxiety are normative globally and therefore a normal part of living. Violence, political conflict, civil war, terrorism, street violence, and domestic violence—is the trauma from these situations a pathology? Or is it the normal physiological response of normal individuals to the physical, psychological, and moral threats of real danger? Stouffer's study of the American soldier in World War II found a dose-response curve between time in active combat and symptoms of what was then called war neurosis (now post-traumatic stress disorder [PTSD]) (12–14). Combat and killing—often associated with remorse and regret among soldiers—are moral problems that plague many for a lifetime because they are unaddressed by the military medical system.

Large-scale forces shape moral experience. They impinge upon and remake what matters most for ordinary people. How this happens involves the interaction of three very different phenomena: cultural meanings, social experience, and subjectivity (inner emotions and sense of self). As each one of these aspects changes, so too do the others. So when the reservoir of cultural images in our society changes, so too does the sense of who we are (Fig. 1).

Cultural Transitions

Global changes (e.g., major changes in the economy, the rise and fall of governments and institutions, natural and social disasters, and the reordering of life after a catastrophe) can dramatically alter the cultural meanings that people take for granted. They alter the way that people view the world, envision the future, and think about themselves. They help shape the stories people tell and the images they amass to represent their experience. One need only compare Marcovolado's renditions of the crucifixion in the thirteenth-century with Picasso's in the twentieth-century. There is the gradual abstraction of form and meaning in Picasso's pictorial rendition of dehumanization and the disoriented and disorienting force of large-scale changes. Picasso's is an ensemble of shapes and lines, yet with no sure semblance of a suffering body. It is as if the human itself—in the aftermath of the Great War and in the period of the threat of fascism—has been taken out of what suffering means.

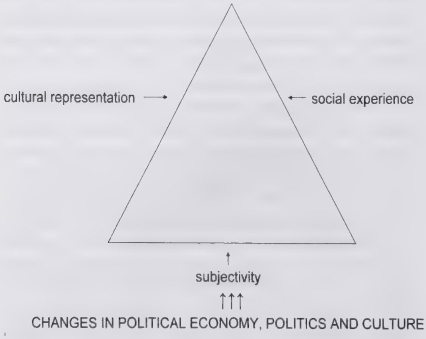

Fig. 1. The remaking of moral life.

These images tell us about major changes that are taking place right now. In our times, suffering, illness, and affliction are abstracted from experience. They are made into lines, shapes, and graphs. They become merely technical conditions (they can be charted, mapped, and coded). And as this shift in cultural representations occurs, the experience of suffering alters. Among the unintended consequences is that the experience of illness itself begins to "thin out," it loses its humanity. Anthropologists have revealed the great diversity and force of what suffering means across human societies. Affliction and suffering are endowed with enormous aesthetic, moral, and religious significance. Healing is a shared process of subjective, bodily, and worldly transformation. Ritual experience, transformations of the body and of the mind, religious transformations, and the somatic expression of pain, violence, and trauma—these universal phenomena make illness a foundational human experience, something that is shared as the existential core of what it means to be human.

This aesthetic, moral, and emotional meaning is purged when suffering and illness are recast solely in biomedical disease categories (15). Medicalization—the making of the social world into abnormality and foci for treatment—is among the most blatant examples of how the sense of human life is being fundamentally remade in medicine (16)[1]. Ordinary unhappiness and bereavement is remade into clinical depression, existential angst into anxiety disorder, and the moral experience of violence, upheaval, and catastrophe into PTSD. Many American psychiatrists define normal bereavement as lasting for only several months, but the anthropological literature is filled with examples of normal bereavement regarded as lasting years, decades, lifelong (17–20). There is simply no scientific evidence to support the American Psychiatric Association's DSM criterion for normal bereavement as lasting two months. This remarkable example of cultural change is propelled as much by the political economy of the pharmaceutical and health insurance industries as by the unexpected consequences of technological innovation.

---

[1] "Medicalization" refers to a few processes whereby the scope of biomedical expertise is expanded. There is an increase in the number and kinds of attitudes and behaviors that have come to be defined as illnesses. There is a shift from discourses of sin, crime, and deviance to illness and disease categories. Health, illness, and medicine are now major portions of gross national product.

Quietly but ineluctably, beneath the surface of events large and small, the self itself is changing. We are not the same people as our parents or grandparents, and our children will not be the same people we are. The self is being thinned out. It is being emptied of the shared human core of life, a transition deftly captured in Picasso's abstraction. In its place there are now processes that lead us to a sense of who we are largely as consumers of things, including drugs, and with a thin, technological view of the world, ourselves, and others. The self is today "filled" via a prescription, and the ongoing, back and forth practice of prescribing and taking drugs makes sufferers into believers of disease as much as consumers of chemicals. Medicalization makes unhappiness, anxiety, and moral anguish things that should not happen, that are not normal, and pharmacology as an end in itself could end up undermining our human ability to cope with these very normal and serious conditions.

Doctor-Patient Relationship as Culture in Transition

All of this adds up to a major change in the doctor-patient relationship. The crisis of the uninsured, commitments to efficiency versus quality, to markets versus moral concerns—this relationship is more and more becoming a bureaucratic imperative rather than a Hippocratic one. And for sufferers, this culture itself can seem dangerous. The experience of this 65-year-old man with worsening diabetes and associated kidney, visual, and metabolic problems is not uncommon:

> They rush me in for a visit. There is hardly time to talk about what is happening. No one asks anymore how I am feeling. And then I am rushed out. I don't get a chance to tell all that has happened. Or even to ask about what is coming next. I am very angry and very disappointed. What good does it do?

For the French philosopher Emmanuel Levinas, suffering is primarily a moral issue. The first task of any caregiver is acknowledgement. One legitimates the reality and seriousness of what is going on for the sufferer (20). This involves a face-to-face encounter in which moral issues take precedence over scientific, cultural, or economic ones (21). This demands that the caregiver go beyond cultural stereotyping, for this would be an obstacle to engaging on a more existential level. On an existential level, doctors interact with patients as individuals who each have something at stake, not simply as technical experts standing over and above cultural stereotypes. The explanatory models do not ask, "What do Haitians call this problem?" They offer a direct appeal to an individual, asking the patient, "What do *you* call this problem?"

For Levinas, this direct appeal means that the moral burden of suffering lies not with the sufferer herself, but with the caregiver. In making a direct appeal, the caregiver is affected by the response given. The caregiver becomes a sufferer as well, who first acknowledges and then intimately experiences what is at stake for the other person. In this way, suffering is shared, if not as psychological or physical reality then as moral experience. It is validated as something that matters, for the sufferer and the caregiver alike. One of the great images of suffering is Michelangelo's *Pieta* (1500). It depicts the Virgin Mary holding Christ's body after his death. What shines forth in this image is not so much Christ's own suffering. It is the suffering of the Virgin. To say that we suffer on behalf of the other does not imply that the immediate physical experience of suffering is devoid of meaning. To the contrary, it affirms the seriousness, significance, and gravity of the situation *for the sufferer*.

The kind of empathy and mutuality of affliction that Levinas idealized is rare. And trends in global culture, the media, institutions, and even biomedicine are making it rarer. With large-scale changes, as we have noted, the self also changes, so that what we believe, how we act together, and who we are as individuals also becomes something new. And that change extends to how we regard ourselves and others. The affinity between people is changing. The relationship between doctors and patients turns on expertise, technical mastery over disease and distress, and the prescription of treatments. But patients and doctors perceive each other with ever-increasing wariness, distrust and ambivalence. The culture of our time becomes an obstacle: bureaucratizing, distancing, and auditing professional relationships.

Medicalization itself becomes an obstacle in human relationships. It makes neat groups of people who either do or do not have certain disorders, rather than people who participate in common experiences, such as unhappiness, fear, distress, and social transformation. It is more difficult to understand how calamities large and small affect ordinary people when ordinary suffering is recast in terms of medical pathology. Three quarters of hospitalized terminally ill patients in the last weeks of life have most of the symptoms of DSM-IV depression based on inanition, symptoms of disease, effects of medication, and response to terminal care. In our view, they are not clinically depressed. They are experiencing serious suffering, a crucial moral condition: one that doctors of past generations recognized and dealt with as fundamental to living and dying with meaning. Calling them depressed is often a conversation stopper—time for antidepressant drugs. When what is often needed is a conversation opener so that people at the end of life can express and explore the most tellingly human of fears and concerns.

Picasso's painting, *Head of a Medical Student* (1907), speaks to the moral crisis in medicine today (Fig. 2). With one eye opened and one eye closed, the medical student is not really facing the world. And it is as if the expertise and technical skill that training cultivates depends precisely on this aspect of detachment. Hence, this is an image of cognition, mastery, and knowledge, all conveyed in the head. This representation is different from the *Pieta*, then, giving us an image of a *partial* or *half* witness. A lineage of artistic works in which doctors and patients are situated beside one another culminates, in the modern period, with this image of a medical student, without patient or context. The doctor becomes the isolated subject of medicine (and the subjectivity of suffering, its lived experience, is outside the frame). Consider the following words, given by a 39-year-old college teacher with a chronic intestinal condition.

> You would think I was irrelevant to my disease from the way I get treated. Nobody asks me about my ideas. When I make a suggestion, it's taken as if it came from left field. It makes me angry, and it makes me want to do something, anything really to show them that I am part of this. Sometimes I purposefully miss an appointment or don't comply with the treatment, as silly and futile as that is. I'm sore because I want to have my opinion respected, taken into account.

Today, patients show resistance to doctors because of the bureaucratic indifference and cold treatment they experience at clinics. The rising cost of health care makes one's own biology into a luxury and a lifestyle. And the deeper sense among sufferers that there is more to illness than a five-minute work-up brings into relief the economic, moral, and social shortcomings of biomedicine. The model of a caregiver who sufferers on behalf of the suffers, developed by Levinas, runs contrary to the culture of biomedicine and its institutions, a culture so deftly captured by Picasso. It recasts suffering as something that is shared between two people. And that way it should be more culturally appropriate to the worlds of care giving. But perhaps not any longer in America.

We are suggesting here that in addressing culture, biomedicine needs to come to terms with the moral conditions that culture signifies and also with the reality that the culture of patients and doctors is going through an epochal shift. Therefore culture cannot be dealt with via timeless stereotypes of members of racial, ethnic, and other social

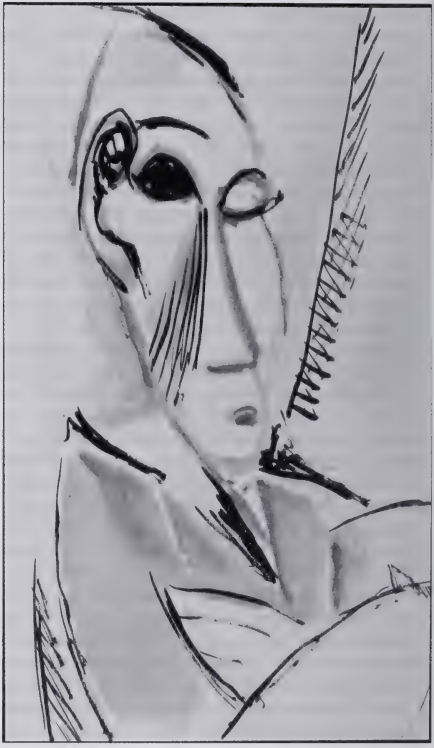

Fig. 2. Picasso's Head of a medical student" (1907).

groups. If culture is about what is at stake for patients, families, and doctors, then doctors need to be trained to inquire about what is at stake in illness and treatment, and to respond to what they learn about patients in their local worlds. Whether the patient is Russian, Haitian, or Dominican, or the practitioner is Arab, Chinese, or Indian, the focus needs to be on the vital cultural condition that connects their moral experiences, which in truth is our human condition, and therefore the basis for humane care.

This is what doctors need to cultivate side by side with technical competence. At present, one of the powerful consequences of global culture is the impediments it creates for cultivating the humanity of the patient *and* the doctor.

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Left Ventricular Remodeling after Myocardial Infarction:

Past, Present, and Future

Satish R. Tiyyagura, M.D.[1], and Sean P. Pinney, M.D.[2]

Abstract

Medical advances in the care of cardiac patients have resulted in more patients surviving an acute myocardial infarction (MI) than ever before. Each year hundreds of thousands of these survivors undergo remodeling of their left ventricle and often progress to clinical congestive heart failure. The extent of remodeling has been linked to the size of the infarct, whether or not the myocardium has been revascularized, and the control of loading conditions. The extent of infarction can be measured several ways, including the amount of enzyme released as well as infarct imaging with nuclear perfusion or magnetic resonance imaging. Methods to prevent adverse remodeling of the ventricle have included pharmacotherapy with beta-blockers, nitrates, and modulators of the renin-angiotensin-aldosterone system. Surgical intervention has proven useful for select patients with aneurysmal areas of remodeling. Researchers are now investigating several approaches to preventing and reversing cardiac remodeling. These include the use of stem cells to regenerate myocardium and post-infarct pacing to prevent remodeling. Improved therapies are needed to help reduce the number of patients progressing from myocardial infarction to end-stage heart failure.

Key Words: Heart failure, left ventricle, remodeling, myocardial infarction.

Introduction

It is estimated that 1.2 million Americans had a myocardial infarction and 500,000 died in 2005 (1). Approximately 7.8 million people in the United States have survived an MI. Their hearts undergo adaptive responses to the change in hemodynamics as less myocardium attempts to maintain the same cardiac output as before. The remodeling that occurs begins immediately and may continue for a lifetime (2). While this adaptive remodeling seems beneficial in the short term, over time it becomes deleterious, leading eventually to congestive heart failure.

The cost of treating acute MIs is enormous: it was $140 billion in 2002 (direct and indirect costs combined) (3). When the costs of congestive heart failure are added to the equation (direct cost of $22 billion), the consequences of remodeling are better appreciated. Fortunately, there are therapies to reduce post-MI remodeling.

Pathophysiology

The responses to myocardial infarction are numerous, involving many changes at the cellular and molecular levels. Myocardial cell death requires adjustments to account for the increase in workload of the remaining myocardium. The remodeling that occurs includes dilatation, hypertrophy, scar formation, neurohormonal responses, cytokine activation, and oxidative stress (4–6). The extent of remodeling is proportional to the mass of infarcted myocardium, the patency of the infarct-related artery, and ventricular loading conditions (7).

The responses that occur after an MI can be divided into early and late remodeling, with the former occurring in the first 3 days after the MI and the latter occurring more than 3 days after the MI. Early remodeling occurs mainly in the infarct and peri-infarct zones. Late remodeling includes

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changes in the geometry and size of the entire left ventricle.

One of the early changes in ventricular remodeling is infarct expansion, a phenomenon in which the size of the infarct typically increases in the first few days. It does not involve an increase in myocardial necrosis. Instead, the mechanism is postulated to involve cell rupture, reduced intercellular space, stretching of myocytes, and slippage of myocytes, resulting in fewer cells per wall thickness (8). The degree of infarct expansion ranges from the clinically inapparent to ventricular rupture. Factors such as the location of the infarct, size of the initial infarct, thickness of the infarcted myocardium, and loading conditions on the ventricle, contribute to the likelihood and significance of infarct expansion. Up to one-half of anterior wall MIs show infarct expansion, and there is a clear relationship between infarct expansion and a poorer prognosis (9).

Remodeling in the left ventricle (LV) also includes changes to the healthy myocardium. In response to the change in loading conditions, the entire ventricle dilates (10, 11). The process begins immediately and can last for months after the MI. Mitchell et al. studied 52 patients at 3 weeks and then at 1 year after an anterior wall MI, with biplane ventriculography. The contractile segments of the left ventricle elongated and the LV became more spherical in geometry (12, 13). Specifically, after an anterior MI, the LV apex is the most vulnerable region to undergo remodeling: it is the thinnest area and it increases in radius the most (14). This principle was well illustrated by a subgroup of the HEART (Healing and Early Afterload Reducing Trial) trial, in which patients underwent echocardiographic analysis of wall stress. After an anterior MI, the degree of initial apical wall stress correlated to the degree of LV remodeling that occurred at 90 days (15).

Neurohormonal mechanisms compound the alterations in hemodynamics and the remodeling that occurs. The sympathetic nervous system, via norepinephrine-mediated activation of reactive oxygen species and tumor necrosis factor (TNF), has been implicated in inducing apoptosis in cardiomyocytes (16). The further loss of cardiomyocytes contributes to progressive LV dilatation. Another major system that has enhanced activity after an MI is the renin-angiotensin-aldosterone system (RAAS). The body responds to the diminished cardiac output just as it would to blood loss or dehydration. Renin levels are markedly increased, angiotensin II is activated, aldosterone is released, and vasopressin is increased. All of these effects serve to increase plasma volume, decrease sodium excretion, and increase vascular tone. Within the region of the myocardial infarct, aldosterone increases the deposition of collagen. These two systems—the RAAS and the sympathetic nervous system—play an important role in the changes that occur after an MI. The Figure illustrates the complex interplay between these and other systems that occurs during remodeling.

Infarct Imaging

While a comprehensive review of infarct imaging is beyond the scope of this article, a brief mention is warranted. Determining the location and extent of the infarct provides important prognostic information for the management and therapy of the patient. The most common modalities are echocardiogram, radionuclide angiography, and single photon emission computed tomography (SPECT) imaging. While all of these modalities have been used in clinical trials with good reproducibility, in clinical practice they are less precise. The introduction of cardiac magnetic resonance (CMR) has brought a technology capable of increased sensitivity, increased reproducibility, and better resolution.

In a study of 91 patients with known or suspected coronary artery disease, SPECT and CMR were compared to determine sensitivity and specificity of infarct detection. For subendocardial infarcts SPECT was inferior to CMR imaging (SPECT missed 13%), but it was as good as CMR for transmural infarcts (17). Another area where CMR can have prognostic significance is in evaluating microvascular reperfusion. Abnormalities in microvascular perfusion can occur despite patent coronary arteries. Contrast enhanced CMR with first pass perfusion can demonstrate regions of microvascular obstruction, which correlates with decreased wall motion and increased clinical events (18, 19).

The advantages of CMR can be important clinically; however, the practical application is somewhat limited. Due to the expense, time, and expertise needed to provide and read CMR, only a limited number of centers would be able to perform the studies. For large numbers of patients, echocardiography will still be more available and cost-effective despite any shortcomings.

Pharmacotherapy

Nitrates

Nitroglycerin was first discovered to have pharmaceutical properties in 1847 by Ascanio Sobrero. Since then the fortunes and careers of several men, including Alfred Nobel, Ferid Murad,

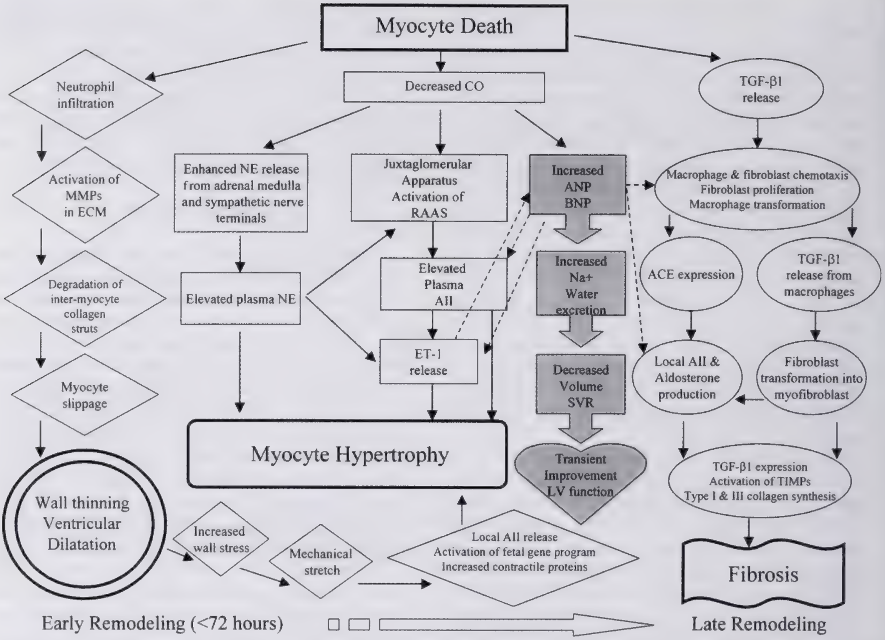
Myocyte Death
Neutrophil infiltration
Decreased CO
TGF-β1 release
Activation of MMPs in ECM
Enhanced NE release from adrenal medulla and sympathetic nerve terminals
Juxtaglomerular Apparatus Activation of RAAS
Increased ANP BNP
Macrophage & fibroblast chemotaxis Fibroblast proliferation Macrophage transformation
Degradation of inter-myocyte collagen struts
Elevated plasma NE
Elevated Plasma AII
Increased Na+ Water excretion
ACE expression
TGF-β1 release from macrophages
ET-1 release
Local AII & Aldosterone production
Fibroblast transformation into myofibroblast
Myocyte slippage
Decreased Volume SVR
Myocyte Hypertrophy
Transient Improvement LV function
TGF-β1 expression Activation of TIMPs Type I & III collagen synthesis
Wall thinning Ventricular Dilatation
Increased wall stress
Mechanical stretch
Local AII release Activation of fetal gene program Increased contractile proteins
Fibrosis
Early Remodeling (<72 hours)
Late Remodeling

Figure. Proposed mechanism of cardiac remodeling, demonstrating the many factors involved in the pathophysiology of ventricular remodeling. ECM = extracellular matrix; RAAS = renin-angiotensin-aldosterone system; CO = cardiac output; SVR = systemic vascular resistance; LV = left ventricular; AII = angiotensin II; NE = enhanced norepinephrine; TGF = transforming growth factor; ET = endothelin; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; TIMP = tissue inhibitor of metalloproteinase.

Reproduced with permission from Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation 2000; 101:2981–2988 (5).

Robert Furchgott, Salvador Moncada, and Louis Ignarro (among others), have been closely tied to it. Nitrate-based therapies for acute myocardial infarction have been widely used for several decades. Nitrates have several pharmacologic effects: dilatation of the venous system, which results in decreased preload on the left ventricle; mild arterial dilatation, which results in decreased afterload; and selective dilatation of coronary arteries, which can result in increased myocardial perfusion to the peri-infarct zones. These hemodynamic effects are said to be responsible for limiting infarct size, reducing infarct expansion, and improving ventricular geometry in post-MI patients (20–22). At the molecular level, nitroglycerin effects these hemodynamic changes by its ability to produce nitric oxide, which activates soluble guanylyl cyclase, which in turn produces cyclic guanosine monophosphate (cGMP) and results in decreased intracellular Ca^{++} and vasorelaxation of smooth muscles (23–25). The clinical benefits of increased perfusion include a decrease in ischemic injury and a decrease in infarct size. The beneficial effects are more potent when there is no evidence of clinical hypotension (26). In one trial, the addition of a vasoconstrictor abolished the positive effects of intravenous nitrate therapy, demonstrating that it is mainly the hemodynamic effect of nitrate therapy that is clinically relevant (27).

A meta-analysis done in the pre-thrombolytic era showed a small mortality benefit to nitrate therapy in acute MI, although two large randomized trials in the mid-1990s (GISSI-3 and ISIS-4) did not show a statistically significant benefit (28–30). However, there was significant crossover use of nitrates in the control arms of both studies, which may have exaggerated the benefit of placebo. Despite the shortcomings, there was a very statistically significant (p<0.001) decrease in early mortality (Day 0–1) in the nitrate-treated arm of ISIS-4, but this effect dissipated with chronic therapy (30). The most current recommendations of the American Heart Association (AHA) for the treatment of acute myocardial infarction, published in 2004, give a class I indication for the use of nitroglycerin by patients with ischemic discomfort, hypertension, or pulmonary congestion (31). While nitroglycerin is still an important therapeutic agent, it has been relegated to a secondary role compared to angiotensin-converting enzyme inhibitors (ACE-I) and beta-blockers.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

ACE-I's work by blocking the conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor. ACE-I's also block the degradation of bradykinin, which is a mild vasodilator. Angiotensin II has effects that can be deleterious, including sodium and water reabsorption, systemic arteriolar constriction, endothelial dysfunction, increased sympathetic tone, and left ventricular hypertrophy (32–35). A number of angiotensin II receptors have been identified. Most of the hemodynamic effects attributed to angiotensin II are related to its binding to the angiotensin 1 (AT1) receptor.

After a myocardial infarct, levels of the ACE enzyme in the cardiac tissue of rats are elevated (36). Animal studies in the 1980s with the ACE inhibitor captopril showed its potential benefits: in preventing hypertrophy, diminishing already established hypertrophy, and preventing LV dysfunction (37, 38). ACE inhibitors have been found to modulate the increased fibrosis that is seen with activation of angiotensin II, resulting in a more functional myocardium (39). They also improve the hemodynamics after an MI by effecting decreases in afterload and preload. They decrease left ventricular filling pressures by inducing venodilatation and enhancing myocardial relaxation. ACE inhibitors dilate the arterial system and thus lower afterload, in part by the resulting accumulation of bradykinin. Many of the hemodynamic effects of ACE inhibitors have been duplicated in similar studies using angiotensin receptor blockers (ARBs). These drugs offer a more selective blockade of angiotensin II, resulting in fewer side effects, such as the cough mediated by bradykinin.

In addition to improvement in indices of LV remodeling such as LV size, volume, and function, several large clinical trials have showed mortality benefit to using ACE inhibitors after acute MI (40, 41). In the Survival and Ventricular Enlargement (SAVE) study, Pfeffer et al. enrolled 2,231 patients with subclinical LV dysfunction (LVEF < 0.40) between 3 and 16 days after an MI and divided them into a captopril arm and a placebo arm. After 42 months of follow-up, the patients with captopril had a 19% reduction in death (20% vs. 25%), a 25% reduction in recurrent MI, and a 37% reduction in risk of severe congestive heart failure (CHF) (42). Similar results were obtained with the ACE inhibitor trandolapril (TRACE study), with a relative reduction in death at 3 years of 18% (35% vs. 42%) and a strong reduction in progression to severe CHF as well (43). The findings of these early trials have been mostly confirmed by later trials and several meta-analyses have confirmed the mortality and CHF benefits of ACE inhibitors (44–46). Despite the overwhelming evidence supporting their use, clinicians should use judgment on when to initiate therapy. In CONSENSUS II, enalapril was given intravenously on the first day after MI to over 3,000 patients. At 30 days and 180 days, there was a trend towards higher mortality in the enalapril group (7.2% vs. 6.3% and 11.0% vs. 10.2%). The lack of efficacy may be explained by a 12% rate of hypotension in the enalapril group (3% in the placebo arm) (47).

Angiotensin receptor blockers are a newer class of drug than ACE inhibitors and still require more pre-clinical and clinical data to support their use for LV remodeling after MI. Nonetheless, the appeal of a selective drug to block one culprit receptor is undeniable (48–51), especially when some studies have indicated that ACE inhibition is sometimes not complete and diminishes over time. In addition, alternate pathways of angiotensin II generation have been described (52–54). Some studies have also suggested that activation of other AT receptors (e.g., AT2) may actually have beneficial effects opposing cardiac remodeling (55). Unfortunately, clinical trials with ARBs have a disadvantage in comparison to the older ACE inhibitor trials, since patients are much more aggressively treated now after an MI. Thrombolysis, coronary ince intervention, beta-blockers, ACE inhibitors, statins, and anti-platelets agents are more frequently used than in the past. To date, there are two large multicenter trials that have evaluated ARBs in post-MI patients. Neither one has been overwhelming.

The OPTIMAAL trial, which investigated the effects of losartan and captopril on mortality and morbidity in high-risk patients after acute MI, randomized 5,477 patients with ST-segment elevation MI (STEMI), re-infarction, or heart failure during the acute phase to a target dose of either losartan 50 mg once daily or captopril 50 mg three times a day. All-cause mortality was non-significantly in favor of captopril (16% vs. 18%; p=0.07) (56). The negative results of OPTIMAAL were surprising in light of the theoretical benefits of ARBs, and clinicians were left to conclude that ACE inhibitors were preferable to ARBs for post-MI patients, but that ARBs could probably be used by those intolerant of ACE inhibitors. One criticism of OPTIMAAL was that the dose of losartan may not have been high enough.

VALIANT (valsartan, captopril, or both in MI complicated by heart failure, LV dysfunction, or both) was completed by Pfeffer et al. soon after OPTIMAAL; it enrolled over 14,000 patients to one of three arms: valsartan 160 mg twice a day, captopril 50 mg three times a day, or valsartan 80 mg twice a day with captopril 50 mg three times a day. The population was moderate-to-high risk with either clinical heart failure or reduced ejection fraction (EF) after an acute MI. After 24 months of follow-up, there was no statistical or meaningful difference in mortality in the three arms (19.5 vs. 19.9 vs. 19.3%) (57). Unlike OPTIMAAL, non-inferiority was proven. Once again it was disappointing that the combined effects of ACE inhibition and AT1 blockade did not translate into improved clinical outcomes. These results were also confirmed anatomically by the VALIANT-Echo study. A 610-patient subgroup of the VALIANT population was enrolled to have baseline and follow-up echocardiograms. Just as there was no difference in hard endpoints, there was also no difference in LV volumes, infarct segment length, or EF on at 20 months between the three groups (58).

Much data has accumulated thus far, providing the benefit of ACE inhibitors in post-MI remodeling and mortality. In light of OPTIMAAL and VALIANT, the data for ARBs is much weaker. Certainly, a patient who does not tolerate ACE inhibitors can use an ARB with some level of comfort, but the ARB should probably not be used as primary therapy. It is also now reasonable to use both if needed for blood pressure control, but such use may be limited by the side effects from combined therapy.

Aldosterone Antagonists

Aldosterone serves an important role in volume homeostasis by preventing the loss of sodium and water when it is activated. It also serves a role in inflammation and repair by activating macrophages, inducing cytokines, stimulating fibroblasts, and increasing the synthesis of type I and III collagens in scar tissue (59–61). It is activated by, and works in coordination with angiotensin II. The simplest description of the RAAS system is that angiotensinogen is cleaved by renin to angiotensin I, which is then converted by ACE to angiotensin II, which in addition to its own vasoconstrictor properties, causes the activation of aldosterone. This would mean that the ACE inhibitors should abolish the effects of both angiotensin II and aldosterone. Unfortunately, it appears that the initial strong inhibition of aldosterone by ACE inhibitors diminishes with chronic therapy (62, 63). This would make the inhibition of aldosterone a desirable target to inhibit cardiac remodeling (64–67).

Inhibiting aldosterone directly in addition to ACE inhibitor therapy was first evaluated in a study of patients with New York Heart Association (NYHA) Class III and IV chronic heart failure. The RALES trial enrolled 1663 patients to usual care plus 25 mg a day of spironolactone. The trial was ended early after 2 years of follow-up due to a very strong 30% reduction in mortality for patients who were enrolled to spironolactone (35% vs. 46%) (68). In a 261-patient substudy of RALES, serum markers of cardiac fibrosis were measured at baseline and at 6 months. Treatment with spironolactone resulted in reduced mortality only for those patients with elevated levels of procollagen type III amino terminal peptide, a marker of collagen deposition (69). Studies on LV remodeling also demonstrated smaller LV volumes and improved EF for patients administered spironolactone (70).

Although RALES evaluated a population of chronic heart failure patients, and spironolactone had a high incidence of side effects including gynecomastia and sexual dysfunction, the trial gave credence to the benefits of early aldosterone blockade (as seen in animal studies) (71). The EPHESUS trial was designed to determine the effect of eplerenone on post-MI patients. Eplerenone is a selective inhibitor of the mineralocorticoid receptor; its selective action results in fewer side effects. More than 6,600 patients with acute MI, ejection fraction less than 0.4, and heart failure were randomized to optimal medical therapy with eplerenone or placebo (72). After 16 months, there was a 15% relative risk mortality reduction in the eplerenone group (14.4% vs. 16.7%). Significantly, side effects were also dramatically reduced. The effect was impressive, considering that both groups were very well treated with more than 86% on ACE inhibitors, 75% on beta-blockers, 60% on diuretics, 88% on aspirin, and even 47% on statins. Although there was only one trial, the strength of the evidence led the American College of Cardiology and the AHA to give eplerenone a Class I recommendation in its 2004 guidelines for acute myocardial infarction (31).

The RAAS system is a very heavily studied system in the pathophysiology of post-MI left ventricular remodeling. Three separate classes of drugs supported by clinical evidence of their ability to improve remodeling and mortality are now available to antagonize the system. The clinician must now learn how to safely use ACE inhibitors, ARBs, and aldosterone antagonists in post-MI patients without causing undue renal dysfunction, hyperkalemia, or side effects.

Beta-Blockers

Beta-blockers have been proven to be beneficial after acute MI for over 20 years and are strongly recommended by the AHA (73). Their benefits include decreased oxygen demand, decreased afterload, increased coronary perfusion, decreased automaticity, and reduction in the risk of sudden death (74–76). Their early trials occurred before ACE inhibitors were in common use and demonstrated the potent effect of beta-blockers on a relatively low-risk population. Initially, it was believed that beta-blockers would probably be harmful in patients with congestive heart failure (CHF), due to the negative inotropic effects.

In the mid-to-late 1990s, studies found that carvedilol and metoprolol improved the morbidity and mortality of CHF patients (77–80). The putative mechanism involved neurohormonal blockade of excessive sympathetic tone. After the benefits of beta-blockers for CHF patients became apparent, studies were completed showing a similar benefit for patients who had a reduced systolic function in the setting of acute MI (81, 82). While the benefits of beta-blockers were clear, it was uncertain what additional advantage they had when added to an ACE inhibitor and other optimal therapy.

To answer this question, the Effect of Carvedilol on Outcome after Myocardial Infarction in Patients with Left-Ventricular Dysfunction (CAPRICORN) trial was completed, demonstrating the effects of carvedilol on mortality after a myocardial infarction in a high-risk population with a left ventricular EF of < 40%. The trial enrolled 1,959 patients, who were initiated on 6.25 mg twice daily and titrated up to 25 mg twice daily. Although sicker than patients in earlier trials, this was also a much better treated group of patients. Over 97% were using an ACE inhibitor and almost half had received either thrombolysis or angioplasty. The study still managed to show a 3% absolute reduction in mortality at 2 years (12% vs. 15%) (83).

While CAPRICORN looked at the hard endpoints of carvedilol therapy, the CAPRICORN Echo Substudy evaluated echocardiographic parameters of ventricular remodeling in 127 of the patients. Baseline echocardiograms were done before enrollment, at 1 month, 3 months, and 6 months. The group that received carvedilol had significant improvements in EF and decreased left ventricular end systolic volume, demonstrating that carvedilol could inhibit ventricular remodeling even in addition to background ACE inhibitor therapy (84).

It is of course important to use clinical judgment to determine the timing and dosage of beta-blocker administration. The recently published COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) enrolled over 45,000 patients with acute MI into an aggressive beta-blocker regimen or to placebo in addition to usual therapy. The risk of reinfarction and ventricular fibrillation was reduced by 10 per 1,000 treated; however, 11 per 1,000 developed clinical shock (85). Similar to CONSENSUS II, this trial illustrates the dangers of protocol-driven medicine and highlights the need for clinical judgment.

The clinical and echocardiographic improvements in left ventricular remodeling after acute myocardial infarction have been well illustrated in the literature. However, the biochemical mechanisms by which beta-blockers reduce LV remodeling is not clear. Li et al. used a rat model of acute MI treated with carvedilol to evaluate the mechanism of action. Cardiac hemodynamics and measurements of inflammatory markers were done to evaluate the biochemical effect of carvedilol on the mechanisms of LV remodeling. Carvedilol decreased the mRNA and protein expression of proinflammatory cytokines, including TNF-alpha, interleukin (IL)-1B, and IL-6 (86).

Altered calcium metabolism also plays a role in post-MI remodeling (87–89). In post-MI rats, there is downregulation of sarcoplasmic reticulum Ca^{++} adenophosphatase (SERCA) and upregulation of phospholamban (an inhibitor of SERCA), resulting in decreased local pools of the calcium that is needed for proper excitation-contraction coupling. The alterations in SERCA and phospholamban are reduced by both metoprolol and carvedilol, which results in less dilatation and hypertrophy (90).

Statins

The pleiotrophic effects of hydroxymethyl glutaryl (HMG) coenzyme reductase inhibitors, or statins, are now fairly well established (91). They appear to have nonlipid mechanisms that alter endothelial function, coronary plaque stability, thrombus formation, and inflammatory responses. The reductions in the inflammatory marker C-reactive protein (CRP) have been well publicized in the literature (92–95). In addition to their coronary benefits, the anti-inflammatory and anti-oxidant effects of statins act to inhibit LV remodeling after MI. Simvastatin has been shown to decrease the levels of many inflammatory cytokines including TNF-alpha, IL-1b, and IL-6. This is associated with improved echocardiographic parameters of LV remodeling (96). Similarly, atorvastatin was able to inhibit stimulated cardiac fibroblasts from synthesizing collagen (97). The evidence for these benefits is based mostly on *in vitro* and animal studies, but the results are still intriguing.

Rats with surgically induced anterior wall MIs were treated with cerivastatin for 12 weeks. At the end of the study period, the cerivastatin-treated rats had a smaller LV cavity, improved contractility and relaxation, less collagen I mRNA, increased endothelial nitric oxide synthase (NOS) production, and decreased peroxynitrite accumulation (98). Similar studies in post-MI mice treated with fluvastatin showed improved survival, decreased LV volume, improved LV ejection fraction, and decreased matrix metalloproteinase (MMP)-2 and 13 activity. These findings suggest that fluvastatin, and maybe all statins, can improve LV remodeling through inhibition of MMPs that are known to cause infarct expansion and LV dilatation (99).

Statins are also known to improve endothelial dysfunction; the mechanism is nitric oxide dependent. Similarly, the nitric oxide (NO) enhancing properties of statins may also be implicated in LV remodeling. Nahrendorf et al. treated post-MI mice with cerivastatin, and analysis by cardiac MRI showed decreased hypertrophy and decreased LV cavity size. Interestingly, the protective effect of cerivastatin was mostly abolished by the addition of N-methyl-L-arginine methyl ester (L-NAME), which is an inhibitor of NOS (100). This suggests an important role for NO and NOS in the statin-mediated protection against LV remodeling. Similar beneficial effects on LV remodeling via a NOS/NO-dependent pathway were demonstrated with atorvastatin in mice, thus strengthening the argument for a class effect of statins (101). In the present era, when it would be difficult to withhold statins after an MI, there will probably be no large randomized trial to fully determine whether the experimental benefits in remodeling translate to the patient.

Revascularization

Modern care dictates that in acute myocardial infarctions, the occluded artery should be opened as soon as possible, in order to optimize myocardial salvage and improve mortality (102, 103). This has clearly been shown to reduce infarct size and improve hemodynamic measurements of LV function (104). There is some debate as to whether reperfusing an artery that is out of the typical range of thrombolytic therapy has any important clinical implications, the so called “open-artery hypothesis.”

There have been several studies to evaluate whether late reperfusion has any important clinical benefits. Investigators were encouraged when a subgroup analysis of ISIS-3 Trial patients who received thrombolytic therapy between 5 and 24 hours after MI showed a 33% mortality benefit (105). The benefits were thought to be the same as with early revascularization: improved electrical stability, less scar formation, preserved ejection fraction, and less ventricular remodeling. Several small trials have attempted to evaluate the effect of late reperfusion on EF and LV size. Gil et al. evaluated 103 patients randomized to alteplase or placebo 6–24 hours after an MI. Interestingly, there was a more improved EF at 1 month, but no difference by 6 months (104). Topol et al. found similarly conflicting results in 197 patients enrolled in the TAMI-6 trial, who also presented late. LV volumes were preserved, but there was no significant effect on ejection fraction (106). Other trials have had similar unimpressive results (107). Despite the scarcity of evidence of improvement, opening coronary arteries late after the infarct is a relatively common practice.

The Future

Inhibition and blockade of various enzymes and receptors in the RAAS pathway has been the basis of therapy to inhibit LV remodeling to date. There are, however, promising therapies using other modalities. Regeneration of the myocardium has been a “hot topic” paralleling the interest in stem cells. Several different ways to effect new tissue growth are being studied in early clinical trials. Surgical approaches to inhibit remodeling have also been looked at. The CorCap^{TM} device (Acorn Vascular, Inc., St. Paul, MN) has been used with some success in humans with chronic CHF, and is now being evaluated in animals after MI. Another promising therapy involves pacing the left ventricle. The benefits of biventricular pacing have been shown in chronic heart failure; it is now time to investigate its role in post-MI patients.

Cell Therapy

Therapy aimed at modifying the scar left after a myocardial infarction has included experimental cell-based therapies. Initial studies implanted skeletal muscle myoblasts into the scarred region. The myoblasts implanted, but clinical studies revealed unacceptably high rates of ventricular tachycardia and sudden death (108, 109). Indeed, further trials have required the use of amiodarone or an implantable cardiac defibrillator to enroll patients. Observations that adult cardiomyocytes were capable of being replaced by progenitor cells have led to speculation that both bone-marrow-derived and embryonic stem cells may be more effective than skeletal muscle myoblasts (110).

In 2004, the results of TOPCARE-AMI were published; they looked promising. Fifty-nine patients with an acute MI were randomized to intracoronary infusions of circulating progenitor cells or bone-marrow-derived progenitor cells 5 days after the MI. Although it was only a pilot study, at one year it appeared safe to infuse either type of cell, and LV volumes and EF were similar in both (111). As an alternative to direct coronary infusion, the induction of bone marrow progenitor cells by granulocyte-colony stimulating factor (G-CSF) was evaluated as another way to increase the number of progenitor cells in the circulation (112). Unfortunately a small pilot study with 27 patients in Korea showed an increase in coronary restenosis when G-CSF was used (113). This was followed by a larger study of 50 patients in the FIRSTLINE-AMI trial, who were given G-CSF 90 minutes after percutaneous coronary intervention (PCI) for acute MI. Follow-up data on those patients did not reveal accelerated restenosis, and left ventricular size and function were significantly improved at 4 months (114). Another trial, REPAIR-AMI, enrolled 204 patients for a multicenter study that infused autologous bone marrow cells into patients 3–5 days after they underwent primary PCI for an acute MI; the data were presented at the AHA last year (115). The ASTAMI investigators used intracoronary injection of bone marrow cells in 101 patients with anterior wall MI. Six-month data was presented at the recent AHA meeting (116). Despite the early setbacks, it appears that there will be further studies to determine the right type of cell therapy to prevent post-MI LV remodeling through tissue regeneration.

Surgical Restraint Device

The idea of using a restraining wrap or device to prevent LV dilatation and even shrink cavity size presents another way in which to prevent remodeling. A randomized trial using a synthetic mesh (CorCap^{TM}) in patients with advanced CHF undergoing mitral valve surgery demonstrated some reduction in LV size and patient symptoms (117). In the post-MI setting there have been promising animal studies (in sheep) that have shown that the passive restraint device can decrease infarct expansion, improve cardiac function, and interrupt LV remodeling (118, 119). However, until this device can be deployed through a minimally invasive technique, it is unlikely to gain much popularity.

Pacing

Cardiac resynchronization therapy has proven useful for advanced heart failure patients with conduction system disease. It has long been known that electrical dyssynchrony is accompanied by mechanical dyssynchrony. A number of clinical trials have now shown that the placement of bi-ventricular pacemakers improves clinical outcomes, including mortality and morbidity (120). The mechanism for the benefit includes improved contractile function, reduced mitral regurgitation, improved energy utilization, and reverse remodeling (121–123). With the strength of data emerging in favor of resynchronization therapy for chronic heart failure, perhaps the same concepts can prove useful in preventing heart failure after MI.

In pre-clinical studies of left bundle branch block and right ventricular pacing, there have been differences in the myocardial work, nutrient balance, and remodeling related to the proximity to the pacing site (124–126). The myocardium closer to the site of pacing does less work than the more distant myocardium. In the therapy of CHF, biventricular pacing has been found to improve mortality, morbidity and quality of life, and effect reverse remodeling (127–129). If these benefits could be extended to patients with significant anterior wall MIs to prevent remodeling, it would have an important clinical impact on post-MI survival. There is the possibility of having early clinical testing, and preliminary results should be available within 18 months. The study will enroll 60 patients with an anterior MI with creatine phosphokinase of at least 2,000 U/L. The patients will undergo biventricular pacing with the LV lead placed close to the infarct zone. In theory, the infarct zone myocardium will be required to do less work and perhaps undergo less remodeling. If this pacing has benefits when added to ACE inhibition, beta-blockers, and other neurohormonal blockade, then it may have a prominent role in post-MI therapy.

Conclusions

It is clear that new therapies are urgently needed to curtail the progression from myocardial infarction to end-stage heart failure. The most effective therapies will likely be ones that are initiated immediately after an acute MI before long-term changes occur. Until the time comes when we have a single option that is cost effective with no detrimental effects, we will need to use the existing tools that we have. While ACE inhibitors and beta-blockers are being extensively used after an MI, the addition of aldosterone antagonism is lagging behind, due to well-founded physician fears of hyperkalemia and renal dysfunction (130). The near future may bring device-driven pacing therapy or even minimally invasive surgical restraint devices.

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Grand
Rounds

Prevention and Management of Occupational Exposures to Human Immunodeficiency Virus (HIV)

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Abstract

Occupational exposure to blood and other potentially infectious body fluids places health care workers at risk for acquisition of bloodborne pathogens, including the human immunodeficiency virus (HIV). Utilizing appropriate techniques, personal protective equipment, and safer "sharp" technology can minimize the risk of these exposures. When exposure does occur, immediate evaluation and initiation of post-exposure prophylaxis, when indicated. can substantially reduce the risk of transmission of HIV. In this article, the basic concepts of exposure prevention and management are reviewed.

Key Words: HIV, occupational exposure, needlestick injury, precautions, post-exposure prophylaxis.

Background

By the end of 2001, 57 documented cases of occupationally acquired HIV infection among United States health care workers (HCWs) had been reported to the CDC (1). HCWs are at risk for occupational acquisition of HIV and other bloodborne pathogens (such as hepatitis B virus [HBV] and hepatitis C virus [HCV]) when there is exposure to a potentially infectious material by a route that can lead to viral transmission (2). Potentially infectious materials include: blood, any visibly bloody body fluid, semen, vaginal secretions, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid and amniotic fluid, and unfixed tissue. The routes of exposure that are considered to place HCWs at risk for infection include percutaneous injuries and contact of mucous membranes or nonintact skin with potentially infectious material. Direct contact with concentrated HIV virus in the laboratory setting would also be included.

Unfortunately, occupational exposures to potentially infectious materials are not uncommon among health care workers. The International Healthcare Worker Safety Center at the University of Virginia estimated that during 1996 there were a total of 786,885 percutaneous and mucocutaneous exposures to blood and other potentially infectious substances among health care workers in the U.S. (3). The majority of these exposures were the result of percutaneous injuries, the route of occupational exposure associated with the highest risk of transmission of HIV and other bloodborne pathogens. The rate of percutaneous injury (expressed as the number of injuries per 100 occupied beds per year) among HCWs in 48 health care facilities participating in the EPINet surveillance program in 2003 was found to be 26.8 in teaching hospitals and 18.7 in nonteaching hospitals (4). Although several studies have shown that rates of occupational exposures have decreased somewhat in recent years (5, 6), exposures to potentially infectious body substances remain a substantial occupational hazard for health care workers.

The average risk of HIV transmission is approximately 0.3% following percutaneous exposure to HIV-infected blood (7). All percutaneous exposures, however, do not present the same risk of transmission. A case-control study of HCWs who had percutaneous exposure to HIV-infected blood identified several factors that were independently associated with HIV seroconversion among

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the exposed HCWs (8). These factors included: deep injury, injury caused by a visibly bloody device, injury caused by a needle that had been directly in the source patient's blood vessel, and exposure to a source patient who died of the acquired immunodeficiency syndrome within two months after the exposure. This last risk factor is most likely a marker for advanced HIV disease with high-level viremia in the source patient, resulting in a higher inoculum in the exposed health care worker. As compared to percutaneous exposures, exposures of mucous membranes and nonintact skin to HIV-infected blood are associated with a lower likelihood of transmission. The average risk for mucous membrane exposures is approximately 0.09%. The risk associated with exposures of nonintact skin has not been quantified but is thought to be even lower than that associated with mucous membrane exposures (2).

Preventing Occupational Exposures

While post-exposure antiretroviral prophylaxis (which will be discussed later) may substantially reduce the risk of transmission following an occupational exposure to HIV, it does not eliminate the risk of transmission, nor can it completely allay the anxiety that many HCWs experience following an exposure (9–11). In addition, some HCWs receiving post-exposure prophylaxis (PEP) will experience substantial, sometimes intolerable, side effects. Finally, an effective PEP regimen for exposures to hepatitis C virus has not been identified. Thus, prevention efforts must be focused not only on prevention of viral transmission once an exposure has occurred but on primary prevention of exposures as well.

There are a number of measures that can be taken to prevent exposures to potentially infectious substances in the health care setting. These measures, which are described in the paragraphs below, include Standard Precautions (12), work practice controls, and engineering controls. Incorporation of each of these measures into the daily practice of HCWs can substantially reduce the risk of exposure.

Standard Precautions, which replaced Universal Precautions and Body Substance Isolation in the CDC's 1996 Guideline for Isolation Precautions in Hospitals (12), are designed to reduce the risk of transmission of bloodborne and other pathogens and are intended for use during the care of all patients. Standard Precautions apply to anticipated contact with blood, all body fluids, excretions, and secretions (except sweat), nonintact skin, and mucous membranes. The main features of Standard Precautions include hand hygiene and the use of personnel protective equipment such as gloves, gowns, and face protection (i.e., mask, eye protection, face shield), when appropriate, to protect the worker from exposure to pathogens. For instance, gloves should be worn whenever contact with any of the body substances or tissues mentioned above is anticipated. Gowns should be used to protect the HCW's skin and clothing during activities that may result in direct contact with body substances, mucous membranes, or nonintact skin or creation of a spray, splash, or splatter of body substances. Face protection should be used to protect the mucous membranes of the eyes, nose, and mouth during activities in which spray, splash, or splatter of body substances may occur.

Work practice controls reduce the likelihood of exposure to potentially infectious materials by altering the manner in which a task is performed. The appropriate work practice control(s) should be included as part of the training process for all patient care activities and procedures. The Table lists some work practice controls that can reduce the risk of percutaneous injuries in the health care setting.

The term "engineering controls" refers to equipment, devices, or instruments that have been designed so that they remove or reduce the likelihood of exposure. Examples of engineering controls include sharps with engineered sharps injury protection components (e.g., self-retracting needles and lancets), needleless systems, sharps disposal containers, and blunt suture needles.

The federal government mandates that these approaches to reducing the risk of HCW exposure to HIV and other bloodborne pathogens be made available to HCWs by their employer. In order to reduce the health risk to workers whose duties place them at risk for exposure to blood or other potentially infectious materials, the Occupational Safety and Health Administration (OSHA) issued the Bloodborne Pathogens (BBP) standard in

TABLE
Examples of Work Practice Controls to Prevent Percutaneous Injuries

Avoid unnecessary use of needles and other sharps.
Do not recap needles.
Announce all sharps being introduced onto or removed from the field.
Pass sharps only in a designated area ("safe zone").
Disassemble sharp equipment by use of forceps or other device rather than by hand.
Do not hold body tissue with fingers when suturing or cutting.
Do not leave sharps on the field.
When suturing, use a needle of appropriate length for the thickness of the tissue.

1991. The standard was subsequently revised in 2001 in response to the Needlestick Safety and Prevention Act (13). In addition to Standard Precautions, work practice controls, and engineering controls, the document outlines requirements for selection and implementation of new control technology, documentation of percutaneous injuries, and HCW training.

Preventing HIV Transmission after Exposure

Despite efforts to prevent occupational exposures to potentially infectious body substances, HCW exposures to these substances continue to occur. Fortunately, a number of interventions can be taken that may reduce the risk of transmission of HIV following an exposure. The Centers for Disease Control and Prevention have provided guidelines for management of occupational exposures to HBV, HCV, and HIV (2). The guidelines for management of occupational exposures to HIV were recently updated (14).

The first step in post-exposure management is to clean the site of exposure. The site of a percutaneous injury or skin exposure should be cleaned immediately with soap and water. Mucous membranes should be flushed copiously with water (2). The exposure should then be reported using the protocol developed by the facility in which the exposure occurred, so that appropriate evaluation of the source patient and, if indicated, evaluation and treatment of the exposed HCW can occur.

Source Patient Evaluation

At the end of 2003, there were an estimated 925,000 – 1,185,000 persons living in the United States who were infected with the human immunodeficiency virus (HIV) (15). Approximately one-quarter of these individuals were unaware of their HIV infection. The source patient's HIV infection status is invaluable in determining the risk of the exposure to the affected HCW and in determining whether post-exposure prophylaxis (PEP) should be recommended to the HCW. Source patient interviews and HIV testing are key components in the occupational BBP exposure program because, as mentioned above, many persons infected with HIV are unaware of their infection status and others may not routinely disclose their HIV infection status.

Standard HIV testing methods, such as enzyme immunoassays (EIA), are not routinely available around the clock. Thus, the HIV infection status of the source patient has frequently been unknown at the time when initial post-exposure management decisions must be made. Given the evidence that HIV PEP is more effective when initiated early after the exposure (as discussed below), many HCWs have initially been prescribed PEP with discontinuation of therapy if the source patient was subsequently found to be HIV-negative. The development of a new generation of HIV diagnostic techniques that can be performed around the clock, that can provide results within one to two hours, and that have sensitivity and specificity similar to that of EIA has the potential advantages of reducing the number of courses of HIV PEP initiated (16, 17), reducing the number of HIV PEP doses ingested (9) decreasing HCW anxiety and side effects of antiretroviral PEP therapy, and decreasing the cost of HIV PEP for occupational exposures (9).

Unfortunately, the source patient's HIV serological status will not be immediately available for all occupational exposures and may never be available in at least a small proportion of exposures. One situation in which this occurs is that of an exposure that involves an unknown source patient. Proper handling and discarding of sharps, prompt cleaning of blood and other body fluid spills, and labeling of specimens of blood and other potentially infectious body substances will minimize the risk of such exposures. A second situation in which the source patient's HIV status remains unknown is that in which there is an inability to obtain consent for HIV testing from the source patient. In the United States, the requirement for informed consent from the source patient in occupational exposures varies from state to state. In situations in which the HIV status of the source patient is unknown at the time of initial evaluation of the exposed HCW, the decision to initiate HIV PEP must be made taking into account all other data available (e.g., type and severity of exposure, prevalence of HIV in the local community, and patient-specific risk factors for HIV infection).

Post-exposure Prophylaxis

Although data regarding the efficacy of PEP following occupational exposures to HIV are limited, there is evidence that administration of one or more antiretroviral agents to the exposed HCW can substantially reduce the risk of HIV transmission. In a case-control study of health care workers with percutaneous exposures to HIV, logistic-regression analysis found that HCWs who became infected following an exposure were significantly less likely to have taken zidovudine after the exposure than were those who did not become infected (OR 0.19, $p=0.003$) (8). Based on this study, PEP is generally considered to reduce the risk of transmission by approximately 80%. Whether current prophylaxis regimens which involve administration of at least two antiretroviral medications, as opposed to the monotherapy that was typically prescribed during the period of the study, offer additional protective benefits has not been specifically evaluated in the setting of occupational exposures.

Given the limited amount of specific data regarding post-exposure prophylaxis for occupational exposures, data from other settings may help to inform decisions and recommendations regarding occupational exposures to HIV. For instance, administration of zidovudine within 48 hours of birth to infants of HIV-infected mothers significantly reduced the risk of infant infection (18). Animal models may also provide useful information regarding both the efficacy of PEP and the optimal timing and duration of therapy. Animal models of simian immunodeficiency virus infection following intravenous inoculation have found tenofovir (a nucleotide reverse transcriptase inhibitor) to be protective when administered within 24 hours of exposure and continued for 28 days following exposure (19, 20). The effectiveness of tenofovir was reduced if administration was delayed until 48 or 72 hours after exposure or if the duration of therapy was reduced to 3 or 10 days. These findings highlight the importance of immediate reporting of exposures and rapid institution of antiretroviral therapy when indicated.

The decision to initiate post-exposure prophylaxis is based on an assessment of the level of risk associated with each exposure. This assessment should take into account all available information, including the type and severity of the exposure, the source patient's HIV status and/or risk factors for HIV infection, and the prevalence of HIV in the local population (if source patient's HIV status is unknown) (14). Based on available data, when HIV PEP is indicated, it should be initiated as soon as possible after the exposure (e.g., within two hours) and continued for 4 weeks.

When the decision is made to initiate HIV PEP, issues that must be considered during regimen selection include: efficacy of the antiretroviral agent(s), the likelihood that the strain to which the HCW was exposed will be susceptible to various antiretroviral agents, pill burden, and tolerability. HIV PEP regimens typically consist of two or three antiretroviral medications. Current CDC guidelines include recommendations for the use of a two-drug regimen for lower risk exposures and a three-drug regimen for higher risk exposures (14). Other agencies, such as the New York State Department of Health AIDS Institute, have recommended a three-drug regimen for all occupational exposures (21). A detailed discussion of HIV PEP regimen selection is beyond the scope of this article, but abundant resources, such as the CDC guidelines (14), exist for those with additional interest.

When post-exposure prophylaxis is being considered, consultation with an expert is recommended. For those without access to a local expert, an exellent resource is the National Clinician's Post-Exposure Prophylaxis Hotline ([PEPline], 1-888-448-4911), which is operated by the University of California, San Francisco, and provides 24-hour expert consultation to health care professionals managing occupational exposures to bloodborne pathogens. Other agencies, such as state and local health departments and HIV treatment centers, also provide 24-hour consultation services. Individuals involved in the evaluation and management of HCWs with occupational exposures to potentially infectious substances should be familiar with locally available resources.

Unfortunately, the potential benefits of HIV PEP often come with substantial side effects. Drug interactions are common with antiretroviral medications, particularly protease inhibitors, and thus must be considered when selecting a prophylaxis regimen. Side effects are also quite common among recipients of HIV PEP, with reported rates of up to 75% or higher (22–25). The frequency of side effects and the type of side effects experienced are somewhat dependent on the number and class of agent(s) and the specific medication(s) prescribed. Gastrointestinal complaints such as nausea, vomiting, abdominal pain, and diarrhea are among the most commonly reported. Other common complaints include fatigue and headache. More than just a nuisance, these side effects can present a significant barrier to adherence to the prophylaxis regimen. In fact, up to one-quarter of individuals prescribed HIV PEP discontinue therapy due to side effects (23, 24). Extensive counseling, thoughtful selection of antiretroviral prophylaxis regimens, aggressive identification and treatment of prophylaxis-related side effects, and, when necessary, substitution of the offending medication may reduce the frequency of discontinuation.

Counseling and Follow-up of the Exposed HCW

Counseling the exposed HCW is a critical component of any evaluation of an occupational exposure to potentially infectious substances. Topics that should be included in the discussion are: the risk of acquisition of each of the bloodborne pathogens, side effects of any treatments initiated, measures that can reduce the risk of secondary transmission (e.g., abstinence or use of condoms), signs and symptoms of acute HIV infection, and recommendations for follow-up evaluation and testing.

The exposed HCW should have serial testing for HIV antibodies performed for at least 6 months following an occupational exposure. Testing is recommended at the time of the exposure and again at 6 weeks, 12 weeks, and 6 months after the exposure. Follow-up should be extended to 12 months if the HCW acquires HCV through exposure to a source patient co-infected with HIV and HCV (14).

Conclusion

Exposure to blood and other potentially infectious body substances is a relatively common occupational hazard for health care workers. These exposures place HCWs at risk for infection with bloodborne pathogens, such as HIV, and often cause the exposed worker substantial emotional and/or psychological stress. In order to reduce these risks, all health care employers should develop comprehensive exposure control programs that include measures to prevent exposures and reduce the likelihood of viral transmission when an exposure does occur. Some of the key components of these programs include HCW education and training, provision of necessary personal protective equipment and safer sharp devices, source patient testing, and a method by which post-exposure prophylaxis can be initiated rapidly when indicated. HCWs can further contribute to their own safety and the safety of their colleagues by performing duties in a manner that minimizes the risk of exposure, appropriately using safer sharps technology, and promptly reporting any exposures that may occur.

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Grand Rounds

The Changing Library:

What Clinicians Need to Know

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Abstract

Over the last two decades, changes in technology have allowed academic medical center libraries to bring the world of biomedical information to the physician's computer desktop. Because digital libraries have grown so rapidly and in so many ways, some clinicians may be uncertain about the services and resources that are available to them. This article explains how clinical faculty can best utilize their library to support their research and patient care. It addresses some of the most common myths about the "new" medical library, and it highlights innovations in library resources and services that can help physicians to better access, use and manage medical information.

Key Words: Medical libraries, academic medical centers, internet, information services, librarians, physicians, professional practice, continuing medical education, information management.

Introduction

Medical libraries play a central role in information dissemination for their institutions by selecting the most useful and authoritative biomedical publications and making them available to faculty, students and staff to support patient care, research and education. Over the last two decades, changes in technology have transformed the way biomedical information is created, communicated and accessed. Academic health center libraries have moved rapidly to take advantage of new information formats and enhanced information access, creating "digital" libraries and networked systems for their users (1, 2).

These digital libraries have provided clinical faculty with a range of new resources as well as new ways to retrieve those resources. From their computer desktops using a Web browser and Internet connection, physicians now frequently have access to data collections that include thousands of electronic journals and hundreds of electronic books. At Mount Sinai School of Medicine, for example, the Gustave L. and Janet W. Levy Library licensed approximately 3,300 e-journals and over 1,600 e-books in biomedical subject areas in 2005. Clinicians may use information available in online formats that blur the traditional distinctions between books, databases and journals. And many libraries have set up remote access to their collections, allowing physicians to use online resources from their campus office, hospital workstation, and off-campus office computers, whether the physical library is open or closed. Medical information is also increasingly portable—physicians can quickly download, e-mail and save content to computers or personal digital assistants (PDAs), and even beam information from one PDA to another.

Because digital libraries have grown so rapidly and in so many ways, clinical faculty may underestimate the services and resources that are available to them. The converse is also true: physicians

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may feel overwhelmed by the range and variety of information and uncertain about which resources are most useful in their specialty areas. Furthermore, physicians familiar with print journals, standard textbooks and indexes such as *Index Medicus* may be unsure that they are using new databases and information formats efficiently and correctly. Studies have found that while many clinicians have adapted quickly to the new digital environment, at least 59% experience difficulty navigating or searching for medical information (3).

This article explains how clinical faculty can best utilize their library to support their research and patient care. It addresses some of the most common myths about the "new" medical library, and it highlights innovations in library resources and services that help physicians to better access, use and manage medical information.

Modern Library Myths

Myth #1: Everything Is Online

A completely digital library might be on the horizon—but it is not here yet. It is true that almost all academic library catalogs and indexes have been reconfigured as online databases, and that biomedical journal articles published after 2000 are likely to be online. Some biomedical journals, however, are still not being published in digital format. In 2005, for example, of Levy Library's current biomedical journal subscriptions, about 350, or over 25% of print journals and over 9% of both print and online journals, were available only in print. Physicians should also be aware that a vast majority of older articles have not yet been published electronically. A journal article that predates 1995 (or even 2000) is much less likely to be available online than content published within the last few years.

There are exceptions to this rule. Subscribers may access *American Heart Journal* online back to 1925 (volume 1), and *Science* is now available electronically back to 1880 (volume 1). The amount of journal content available electronically will continue to grow as providers transfer journal backfiles into digital format. At this point, though, most libraries still have substantial print collections that are not duplicated online, and clinicians must usually obtain older articles from the library's print journals.

Most medical books are not yet available online, although publishers are racing to make classic texts available. Levy Library's collection of electronic books grew from 974 to 1674 titles, or 72% in 2005 alone, and now includes some core titles in almost all areas of clinical medicine. As a result, faculty may want to check their library's e-book holdings before purchasing a new reference book.

Myth #2: Everything Online is Free

Health sciences libraries seek to provide faculty with authoritative, evidence-based information, and very little of that information is free. To the contrary, the cost of scholarly databases, journals and books is increasing, and libraries must often acquire and pay for both print and electronic information formats. Open access initiatives such as PubMed Central (http://www.pubmedcentral.nih.gov) and Public Library of Science (http://www.plos.org), founded in response to the rising costs of journals, have begun to provide free access to a small number of peer-reviewed medical articles; however, there is often a delay in availability (4). The National Center for Biotechnology Information, a division of the National Institutes of Health, provides a number of free databases, including Medline/PubMed (http://www.pubmed.gov), and offers a small collection of e-books without cost. Most online biomedical information, however, is available only by paid subscription.

An academic health center library's costs for electronic resources are usually based on the number of affiliated faculty members and students at the medical center. In 2003–2004, 127 academic health sciences libraries in the United States and Canada reported spending $177,030,359 on their library print and electronic collections: books, journals, databases and other resources (5). Because resources are licensed for and limited to valid users, clinical faculty must access library resources through the library's Web site, and must authenticate (log on) with a user name and password to use library resources available from off-campus locations.

Myth #3: MEDLINE is Difficult to Use

PubMed, the National Library of Medicine's (NLM's) free search interface for the MEDLINE database, is designed to make the wealth of information in MEDLINE easily searchable by health professionals (6). As the technology underlying PubMed has become more sophisticated, searching has become faster and more intuitive. Fundamental to PubMed's power is Automatic Term Mapping (ATM), an advanced "natural language" program that runs in the background of its search engine. ATM looks for synonyms to the words or phrases in a search query, and then uses a specialized algorithm to broaden the search statement with matching vocabulary.

Clinical Queries is a PubMed service specifically developed to support clinicians' evidence-based practices. Built-in search filters in Clinical Queries retrieve research studies using the best research methodologies for specific clinical question types—such as "therapy," "diagnosis," "etiology," and "prognosis." Type in your clinical keywords, select the appropriate question type and you will quickly retrieve research studies matching your query. PubMed's Related Articles link is another helpful search tool that retrieves citations that are closely related to a selected reference by comparing words from the title, abstract, and subject headings using a specialized algorithm.

Other convenient tools allow researchers to save searches and to e-mail selected citations. A helpful feature introduced in 2005 is spell-checking. Finally, PubMed's LinkOut service dramatically enhances MEDLINE's functionality by linking from the MEDLINE database to the full text of many journal articles. LinkOut and other article linking services will be described in more detail below.

Myth #4: Google Can Replace MEDLINE Databases

While Google is a valuable tool, it cannot replace commercial MEDLINE search interfaces provided by companies such as Ovid Technologies or by PubMed. Google (http://www.google.com), the most popular general search engine on the Internet (7), is quick and easy to use. It excels at locating medical news releases, the names of department chairs, or patient advocacy groups. Google also links to some full-text, open-access journal articles, and has even begun to link to MEDLINE citations in PubMed. However, Google has several shortcomings as a search tool for medical information. First, Google results typically contain sponsored links to commercial sites, and its search results often include commercial sites with a promotional focus. As a result, clinicians may find that their searches retrieve irrelevant information. A physician searching www.google.com for "traumatic brain injury," for example, will find several medical malpractice Web sites at the top of the results.

Another drawback to searching Google for biomedical information is that Google searches the World Wide Web, an "ocean" of information of greatly varying quality. A new Google service, Google Scholar (http://www.scholar.google.com), is working with scholarly publishers to limit this ocean to works from research disciplines, but Google Scholar does not identify what publications it covers. Reviewers have also found that Google Scholar's records from known sources such as PubMed often seem to be out of date and/or incomplete (8).

A final problem is that Google and Google Scholar results are retrieved by a formula that places Web sites at the top of results if they have many other Web sites linking to them—not if they are current publications. This relevance ranking formula can be useful if a searcher is looking for a classic article—one that has been cited often by other scholars—or a current article on a "hot" topic that is engendering public comment. Recent publications, however, may be buried within Google's search results (9). Physicians should not rely on Google to identify current, authoritative information to support their clinical practice.

Myth #5: Textbooks Are out of Date before They Are Published

Publishers have begun regularly updating the Web-based versions of some classic textbooks. One example is *Harrison's Online*, which includes daily updates and is always more current than its print counterpart, *Harrison's Principles of Internal Medicine*. Clinicians should also be aware that some texts are enhanced with extra features online. McGraw-Hill's AccessMedicine platform, for example, supplements *Harrison's Online*, *Hurst's the Heart* and their other online textbooks with PDA downloads and access to a drug database, patient handouts and a medical news service.

Changing Library Resources

Keeping Up: Knowledge Synthesis and Current Awareness

"Despair and consternation" about keeping up with medical advances is not new (10). Although the Web has intensified what has long been regarded as a crushing flow of information (11), it has also generated new tools to help clinicians manage the flow. Slawson and Shaughnessy suggest that tools to manage information can be divided into "foraging tools" that alert clinicians to new findings relevant to their practice, and "hunting tools" that allow clinicians to easily find information summaries when they have a question about a patient's care (12).

New hunting tools include the popular "clinical topic review" databases such as UpToDate and eMedicine. These peer-reviewed databases aim to synthesize the current "best evidence" to answer clinical questions at point of care, and are updated daily with the latest research findings (13). Hybrid resources such as MD Consult offer both knowledge synthesis and current awareness, or foraging, tools. Physicians can browse MD Consult features such as "In this Week's Journals" and "This Week in Medicine" to stay informed about the most important new journal articles and medical news. Within MD Consult, they can also search MEDLINE, read some full-text journal articles and review more than 50 full-text medical reference e-books.

MD Consult was among the first medical databases to allow clinical faculty to create customized "personal accounts" as a way of managing the site's information. Database customization, provided by MD Consult, PubMed and others, typically allows physicians to save articles, rerun searches, receive e-mail alerts and announcements tailored to their interests, and even modify the way the database's Web pages are presented. Customization is not limited to databases; many electronic journal distributors offer free e-mailed table of contents alerts and other current awareness services.

Clinicians may have noticed that databases and Web sites are increasingly offering "news feeds" as an alternative to newsletters and e-mail alerts (14). News feeds are also known as RSS feeds, really simple syndication, or rich site summaries. A news reader or "aggregator" is required to use RSS services; many readers, such as Bloglines or MyYahoo, are free to download or to use on the Web. It is not yet clear whether clinical faculty will adapt "news readers" and switch from e-mail updates to "news feeds." PubMed is supporting both options: in 2005 it enabled users to receive updated search results via RSS and via automatic e-mails, and gave extensive publicity to both services (15, 16).

Patient Education and Consumer Health Information

Much has been made of the use of the Internet by patients and its impact on doctor-patient relationships. Clinicians may feel concerned that patients are obtaining information from questionable online resources. They may also feel uncomfortable about managing "expert patients" who arrive at their offices with requests for new and unfamiliar treatments that were uncovered in Web searches (17, 18). Polls show, however, that clinicians are patients' most respected source of health information (19). Most patients want and expect their physicians to interpret the information that they find independently (20).

To help physicians stay abreast of health care news that may be informing (or misinforming) their patients, some health care databases include synopses of reports from the popular press and media. MD Consult, in particular, augments its review of "What Patients Are Reading" with links from news summaries to the professional literature, so that doctors can more easily research the new claims.

Doctors can correct or clarify patients' understanding of their illnesses and treatment choices with evidence-based information, and reinforce their instructions with accurate patient education materials. Many biomedical databases provide patient education resources; Levy Library's database collection, for example, currently includes six products that offer printable patient education handouts. Three of these resources allow handouts to be customized for the patient, and two—MD Consult and MICROMEDEX—include Spanish language leaflets. MICROMEDEX is primarily known as a drug information database, but its patient handout system includes CareNotes as well as DrugNotes. CareNotes covers a wide range of medical and surgical subjects, and the leaflets, written at a fourth to sixth grade reading level, are suitable for low literacy readers.

Physicians can also support their patients by directing them to authoritative consumer health information sources on the Web (21). No directory of consumer health sites would be complete without two library-affiliated information portals: MedlinePlus and the New York Online Access to Health (NOAH). The National Library of Medicine developed MedlinePlus (http://www.medlineplus.gov) to provide access to information produced by National Institutes of Health and Department of Health and Human Services components and other reputable organizations (6). NOAH (http://www.noah-health.org) is a librarian-curated directory to full-text consumer health information, and is drawn from a range of sources (22). Both MedlinePlus and NOAH provide access to information in English and Spanish. Many professional medical societies provide consumer health information; physicians should check their professional association's Web site for consumer health information in their specialty area. Most health library Web sites also provide a list of reputable online consumer health information sources.

Changing Library Services

Full-Text Linking from Databases

The most popular new service offered by academic medical center libraries may be journal article linking. Article linking employs software to allow users to seamlessly connect from one library resource to another. When an article-linking service is implemented, a clinician who finds a journal citation in a database such as MEDLINE, ISI Web of Science or PsycINFO can connect directly to a full-text copy of an article, if available; search the library's online catalog for print holdings; or automatically request the item through an online interlibrary loan system.

In addition to the link resolver services provided by libraries, many databases are also providing their own online links to journal articles. PubMed's LinkOut service is a case in point: LinkOut allows users to connect from PubMed references directly to many full-text journal articles. A library can participate in LinkOut—and increase its usefulness for its patrons—by providing PubMed with a list of its full-text electronic journal holdings. PubMed then adds links customized for the library's subscriptions and identifies them with a button bearing the library logo. The library's customized links (and buttons) are only displayed on a PubMed site available via a special Web address. To take full advantage of LinkOut, then, clinicians must access PubMed through the Web links on the participating library's Web site. Levy Library currently places its PubMed link at the top of its Databases page.

Online Interlibrary Loan Services

Many libraries have replaced their traditional interlibrary loan services with online systems. Clinicians can now enter requests for books or articles not held at their local library without leaving their office, and the requested materials can often be delivered electronically to their desktop. The turnaround time for electronically delivered articles is typically less than that for paper-based systems, and technology upgrades are expected to decrease this time even more.

Bibliographic Management

Gone are the days of handwritten note cards and bibliographies typed by hand. Bibliographic management programs are huge timesavers for researchers and clinicians. Services like EndNote, Reference Manager, and RefWorks are now available through many academic libraries. These tools allow users to organize their research, import references from online databases, automatically produce bibliographies and insert citations into papers. Bibliographic management programs also facilitate collaboration among authors by allowing multiple users to contribute references for a paper to a shared account.

Each program has different strengths. EndNote allows users to embed graphics, including tables and charts, into references and to link them to papers. Both Reference Manager and RefWorks allow clinicians to publish their databases on the Web. RefWorks, an online bibliographic service, allows clinicians to access their personal databases from any computer with Internet access and to connect directly to full-text articles provided through the library. EndNote Web, an online version of EndNote, will be introduced sometime in 2006.

Virtual Reference and Instruction Services

Clinicians increasingly find and use library services and resources without visiting the physical library, and their questions about the library arise outside its walls as well. To support library users, librarians are supplementing in-library reference services with online reference services. Librarians have added e-mail, instant messaging and/or chat services to the telephone and in-person support that they have traditionally offered. E-mail reference allows librarians to provide clinicians with well-researched, detailed answers to their questions. Instant messaging and chat, like telephone and in-person interactions, give patrons immediate feedback. All forms of virtual reference have the advantage of allowing librarians to deliver additional documentation—sample search results, a journal article in PDF format, or an online reference—as attachments to their answer (23).

Physicians and other patrons should note that their library Web site may already provide the answer to their questions about how to use a library resource or service. Librarians are supplementing classroom instruction and reference desk brochures with Web-based tutorials and information guides (24). At Mount Sinai School of Medicine, for example, medical librarians compile and answer "Frequently Asked Questions" (FAQ's); develop customized, hyperlinked resource guides for clinical specialty groups; and offer online instruction on topics ranging from obtaining library cards to conducting database searches. As a result, the library's Web site has become a gateway to its reference and instruction services as well as to its electronic resources. Links to reference services, FAQ's and other library information are usually available from a library's home page.

Summary

The Internet has allowed academic medical center libraries to bring the world of biomedical information to the clinician's desktop. It has also

TOP TEN TIPS
For Getting the Most from Your Medical Library

1. You don't need to visit your library to use your library. Get a user name and password and access your virtual library from your home or office. Most library e-resources are licensed, so make sure that publishers recognize you as a valid user by accessing your library's resources through the library's Web site.
2. Most recent biomedical journal articles are available online; most older articles are available in print only. Virtually all current catalogs and indexes in academic libraries are online. Electronic book collections are growing, too, so check your library's e-book holdings before purchasing a new reference book.
3. Databases such as PubMed are getting "smarter" and easier to use. Many also provide some full-text content, or links to full-text articles. Clinical Queries is a PubMed service that helps clinicians find articles to support evidence-based practice.
4. To find current, accurate information about the latest research and best practices, check resources that cover peer-reviewed journals (e.g., Medline/PubMed) or that provide regularly updated, peer-reviewed, evidence-based summaries (e.g., UpToDate, eMedicine, Harrison's Online). While Google is a valuable tool, physicians should not rely on it to identify current, authoritative information to support their clinical practice.
5. Online resources such as MD Consult are streamlining your ability to keep up with changes in your field—and with what your patients are reading. Many also provide current, clear patient education handouts. And remember, clinicians remain patients' most trusted source of information.
6. Full-text linking is now available from many library databases. A clinician who finds a journal citation in a database such as MEDLINE, ISI Web of Science or PsycINFO can often link directly from the database to an online copy of the article.
7. Faculty can now enter requests for books or articles not held at their local library through online interlibrary loan services. There is no need to leave your office, and the requested materials can often be delivered electronically to your desktop.
8. Bibliographic management programs, available through many academic libraries, can help to organize the references for your publications. They also facilitate collaboration among authors by allowing multiple users to contribute references to a shared account.
9. Your library's homepage is a gateway to your library's services as well as its resources. Check your library's Web site for answers to your questions, guides to using library resources and links to services such as virtual reference and interlibrary loan.
10. Ask a librarian—in person, by phone, by e-mail, or by an online chat service—to show you the quickest, easiest ways to get the best information. Librarians have gone online, so even if you can't come to the library, you can still ask your questions by e-mail as well as by phone, and often via an instant messaging or chat service.

spurred the development of new services and resources that help clinicians find, use and manage information to support their research and patient care. Because online content has grown so rapidly, physicians may underestimate what is available to them or be unsure of how best to use it. A library's homepage is the gateway to its services and resources, and medical librarians can provide guidance online, by phone, or in person on choosing and using the best resources.

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Percutaneous Endoscopic Lumbar Discectomy for Adolescent Lumbar Disc Herniation:

Surgical Outcomes in 46 Consecutive Patients

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Abstract

Background: The surgical outcome of percutaneous endoscopic lumbar discectomy (PELD) for adolescent lumbar disc herniation has rarely been reported on. We performed this study to evaluate the surgical outcome of PELD for adolescent lumbar disc herniation.

Methods: We analyzed the surgical outcomes in 46 consecutive adolescent patients between 13 and 18 years of age (mean age, 16.5 years) who underwent PELD for single level lumbar disc herniation from June 2000 to May 2002. Using the clinical charts and mailed questionnaires, we evaluated the patients preoperatively by the postoperative Visual Analogue Scale (VAS) for back and leg pain, and by the postoperative Macnab criteria.

Results: PELD was performed at L3–4 on one patient, at L4–5 on 40 patients and at L5–S1 on 5 patients. One patient complained of transient dysesthesia after the operation. Another patient underwent subsequent open discectomy because only incomplete decompression was achieved with PELD. At a mean follow-up duration of 37.2 months (range: 25–48 months), the mean VAS scores of both the back and leg pain decreased significantly. In terms of the Macnab criteria, 91.3% of the patients showed excellent or good outcomes. Recurrent disc herniation developed in one patient 14 months after surgery.

Conclusions: Adolescents who underwent PELD for single level soft lumbar disc herniation showed favorable results that were comparable to the results of open discectomy.

Key Words: Adolescent, lumbar, disc herniation, percutaneous endoscopic lumbar discectomy (PELD).

Introduction

Lumbar disc herniation is a rare clinical condition in children. Adolescent lumbar disc herniations are only 1–5% of all the lumbar disc herniations that undergo surgery (2, 3). Open discectomy has been considered a standard treatment for adolescent soft lumbar disc herniation (4–12); however, the long-term outcomes of open discectomy have not always been as good as the short-term outcomes, and a significant number of patients suffer from residual back pain on long-term follow-up (7, 12–15). A minimally invasive surgical technique, chemonucleolysis, has been performed by several surgeons and has showed results similar to or better than those of open discectomy (2, 16–18). However, this technique has not gained popularity because of the possibility of severe complications such as systemic reaction or transverse myelitis (19).

With the rapid evolution of surgical instruments and techniques for minimally invasive spine surgery, percutaneous endoscopic procedures for adult lumbar disc herniation have shown results that are comparable to those of open discectomy, even in cases of recurrent disc herniation (20–30). The main concept of percutaneous endoscopic lumbar discectomy (PELD) has evolved from indirect decompression of the central disc to a direct targeted fragmentectomy (20, 31). Based on the successful results of PELD for adult lumbar disc herniation, we thought that PELD might also be a good treatment option for adolescent lumbar disc herniation. However, the surgical outcomes of PELD for soft disc lumbar herniation in adolescents have rarely been reported on (32). The purpose of this study was to evaluate the surgical outcome of PELD in 46 consecutive adolescent patients with lumbar disc herniation.

Materials and Methods

Patient Population and Outcome Evaluation

A retrospective review was done for 46 consecutive adolescent patients (aged 13–18, middle

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school or high school students in Korea) who underwent PELD for single level lumbar disc herniation between June 2001 and May 2003. The inclusion criteria of this study were as follows: (a) soft lumbar disc herniation was demonstrated on the computed tomographic (CT) scan and/or magnetic resonance imaging (MRI), (b) the patients exhibited radicular symptoms and/or back pain that was consistent with the radiologic findings, and (c) unsuccessful conservative therapy had been administered for at least 6 weeks. Excluded were patients with apophyseal ring fracture, a sequestrated fragment, chronic discogenic back pain and/or severe neurological deficits. Patients with segmental instability were also excluded.

The patients' clinical charts and radiological examinations were reviewed. To analyze the clinical outcomes, we compared the preoperative Visual Analogue Scale (VAS) scores of patients' back and leg pain with their postoperative VAS scores for back and leg pain, and the Macnab criteria (1) were checked via mailed questionnaires. A successful outcome was defined as excellent or good based on the Macnab criteria.

Statistical analysis was performed using the Student *t* test, and two-tailed *p* values less than 0.05 were considered significant.

Surgical Technique

The procedures were performed with the patients under local anesthesia, in the prone position on a radiolucent table. Prior to surgery, the procedure, the patients were informed about all the steps of the procedure. Patients could communicate with the surgeon during the entire procedure.

The skin entry point was usually about 10 – 11 cm from the midline for the L4 – 5 and L5 –S1 levels. For the L3 – 4 level, the skin entry point was usually more medially located than for the L4 – 5 level, i.e., about 7 – 9 cm from the midline. After the entry point was numbed with local anesthetics, an 18-gauge spinal needle was introduced under fluoroscopic image guidance. The final target of the spinal needle was the medial pedicular line on the anteroposterior image and the posterior vertebral line on the lateral image. An epidurogram was then taken with contrast media to confirm the location of the exiting root and the traversing root (Fig. 1A). After insertion of a spinal needle into the disc, an intraoperative discogram was performed with a mixture of 6 mL of contrast media and 1 mL of indigo carmine. The next steps were as follows: (a) a guidewire was inserted through the spinal needle, (b) the spinal needle was removed, (c) a small skin incision was made at the entry site, (d) a tapered, cannulated obturator was inserted along the guidewire (e) after touching the annulus, the obturator was inserted into the disc after the annulotomy was performed (f) finally, a bevel-ended, oval-shaped working cannula was inserted into the disc along the obturator and then the obturator was removed (Fig. 1B, C).

First, manual discectomy was performed through the cannula under fluoroscopic guidance. The endoscope was inserted through the cannula. The blue-stained disc was removed with small forceps and a side-firing Holmium yttrium-aluminum-garnet (Ho:YAG) laser using the 'in and out' technique, that is, working from the central portion to the lateral portion of the disc space on the anteroposterior image (Fig. 1D-F). The herniated fragment had a characteristic feature: the intradiscal portion of the herniated fragment was stained blue with indigo carmine, but the subligamentous portion was only slightly stained by the dye (Fig. 1G). After removing this distinctive herniated fragment, we removed the endoscope and applied a sterile dressing with a one-point suture.

Results

The male:female ratio was 26:20. The mean age at the time of the operation was 16.5 years. Before their operations, 44 of the 46 patients (95.7%) suffered from low back pain and leg pain. Two patients (4.3%) presented with leg pain only. Fourteen patients (20.4%) also showed motor weakness before their operations. All 14 of these patients showed weakness upon great toe dorsiflexion (power grade IV). Three patients (6.5%) had a history of trauma before the onset of their symptoms. The mean duration of the symptoms was 7.7 months (range: 1.5 – 36 months). The spinal levels of PELD were L3 – 4 in one patient, L4 – 5 in 40 patients and L5 –S1 in 5 patients. The demographic findings are summarized in Table 1.

The mean operation time was 51.4 minutes (range: 30 – 75 minutes). One patient (2.2%) complained of transient dysesthesia after the operation. All the patients except one showed improvement of their symptoms immediately after their operations (Fig 2). One patient (2.2%) underwent a subsequent open discectomy because only incomplete decompression was achieved with PELD.

The mean follow-up period was 37.2 months (range: 25 – 48 months). The mean VAS scores of the leg pain decreased significantly after the operations (before operation: 8.52±1.60; at the final follow-up: 1.46±1.57, $p < 0.0001$). The mean VAS score of the back pain also decreased significantly

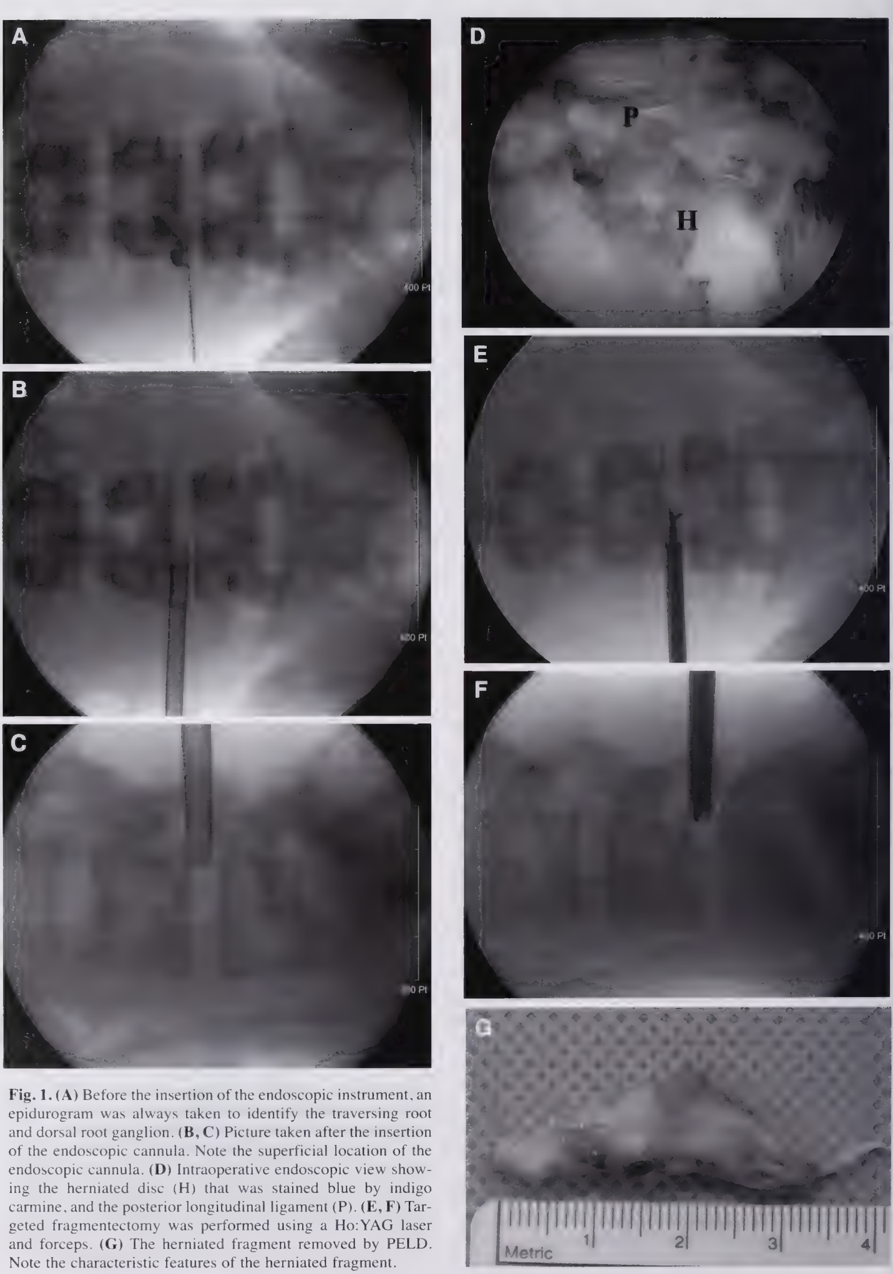

Fig. 1. (A) Before the insertion of the endoscopic instrument, an epidurogram was always taken to identify the traversing root and dorsal root ganglion. **(B, C)** Picture taken after the insertion of the endoscopic cannula. Note the superficial location of the endoscopic cannula. **(D)** Intraoperative endoscopic view showing the herniated disc (H) that was stained blue by indigo carmine, and the posterior longitudinal ligament (P). **(E, F)** Targeted fragmentectomy was performed using a Ho:YAG laser and forceps. **(G)** The herniated fragment removed by PELD. Note the characteristic features of the herniated fragment.

TABLE 1
The Demographics of the Patients Who Underwent PELD

Characteristics	
Number of cases	46
Gender	
Male	26
Female	20
Mean age (years)	16.5
Mean duration of symptoms (months)	7.7 (range 1.536)
Level	
L3–4	1
L4–5	40
L5–S1	5

PELD = percutaneous endoscopic lumbar discectomy.

after the operation (before operation: 7.74±2.38; at the final follow-up: 1.89 ±1.74, $p < 0.0001$). Based on the Macnab criteria, the surgical outcomes were excellent for 10 patients (21.7%), good for 32 patients (69.6%) and fair for 4 patients (8.7%), and so the rate of symptomatic improvement was 91.3%. All 4 patients with fair outcomes showed moderate back pain at the final follow-up (mean VAS score: 5.8) (Table 2). Recurrent disc herniation occurred in one patient (2.2%) at 14 months after his operation. We instituted conservative care, and he showed a good outcome at the final follow-up.

Discussion

With the evolution of such instruments as the endoscope and the Ho:YAG laser, surgical PELD techniques have also advanced very rapidly. As form of minimally invasive surgery, PELD has several advantages over conventional open discectomy. For example, PELD is usually performed with the patient under local anesthesia. Also, the postoperative pain is quite minimal, so patients can usually be discharged within 24 hours after PELD. And during the procedure, the normal paraspinal structures such as ligaments, muscle, lamina and facet joints are preserved. Therefore, the risk of postoperative epidural scar formation and instability can be minimized (20, 33–35).

With children's and adolescents' lumbar disc herniations, the long-term results of disc surgery depend not only on the disc disease itself, but also on the degree of surgical trauma. Mayer et al. recommended that disc herniations in children and adolescents should be treated with minimally invasive procedures (32). They reported on 4 patients who underwent percutaneous endoscopic discectomy for contained or small noncontained disc herniation, all of whom showed excellent or good results. Although we agree with the recommendation of Mayer et al., the number of patients in their report was very small. Moreover, the surgical instruments and techniques of percutaneous endoscopic procedures have improved significantly since the time of their report. Thus, we believe that the present study is the first large series about PELD in adolescents that reflects the current state of percutaneous endoscopic surgery.

In the present study, the surgical outcomes of PELD in adolescents were satisfactory, i.e., 91.3% of all the patients showed successful outcomes at a mean follow-up of 37.2 months. The surgical outcomes in the present study were nearly the same or better than those of open discectomy in adolescents (4–12). When performing percutaneous endoscopic procedures, proper patient selection and narrow inclusion criteria are the most important factors for obtaining successful outcomes (20). Improper selection of patients can result in incomplete decompression and subsequent open discectomy, and this can sometimes result in a poor surgical outcome. Several highly experienced endoscopic surgeons have recently expanded the indications for PELD and have reported successful outcomes even in cases of migrated disc herniation (36). However, the learning curve of PELD is usually steep and the clinical outcomes are especially affected by the surgeon's skill and personal tech-

TABLE 2
Summary of the Patients with Fair Outcomes

Gender/Age	Sx duration (months)	Level	VAS (pre)		VAS (post)		Follow-up (months)
			BP	LP	BP	LP	
M / 15	5	L4–5	10	10	7	7	44
M / 17	1.5	L4–5	5	5	5	4	41
F / 17	24	L4–5	8	9	5	2	38
M / 17	5	L5–S1	6	8	6	2	28

BP = back pain; F = female; M = male; LP = leg pain; pre = preoperative; post = postoperative; Sx = symptom; VAS = visual analogue scale.

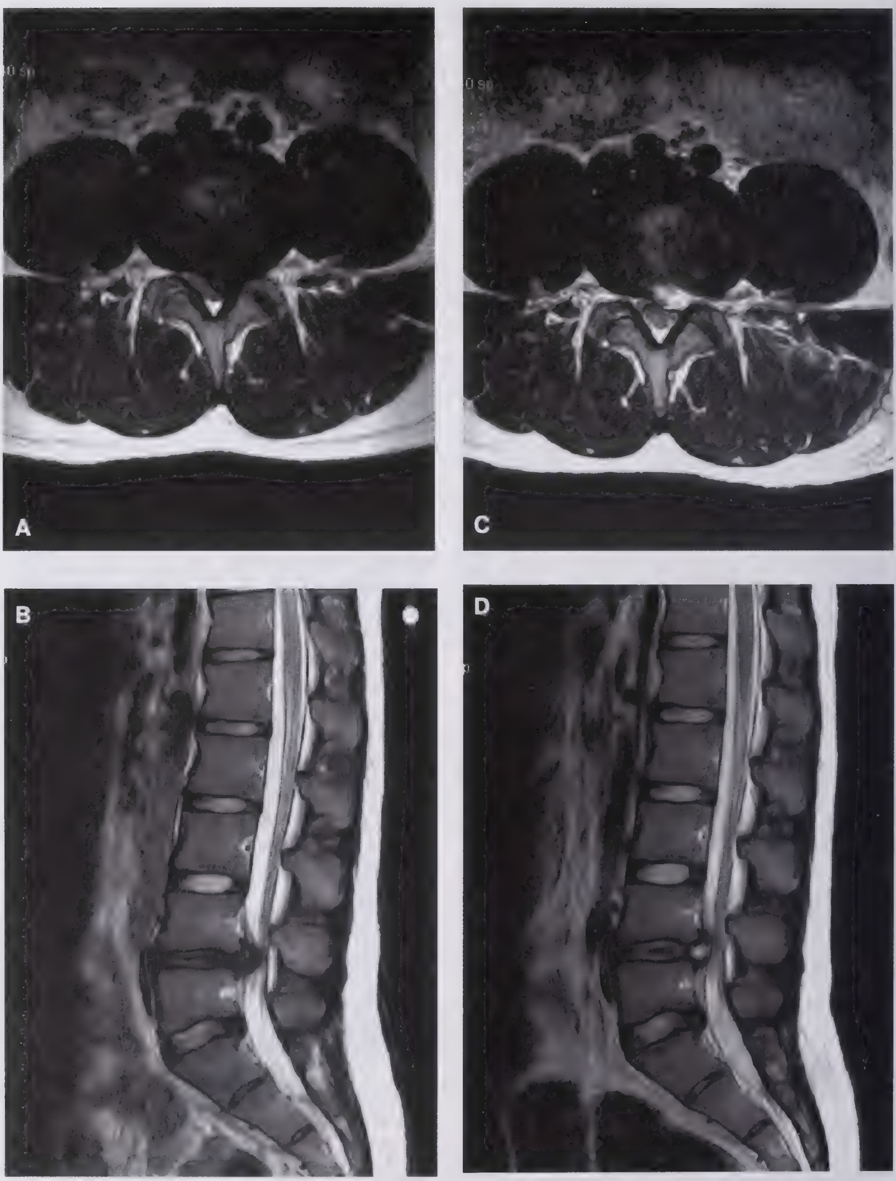

Fig. 2. An 18-year-old boy suffered from back pain and left leg pain for 6 months. His symptoms immediately improved after PELD. The preoperative **(A, B)** and postoperative **(C, D)** magnetic resonance images show the effective result of targeted fragmentectomy.

nique (20). Therefore, in this study we adopted narrow inclusion criteria, i.e., soft disc herniation with radiculopathy with/without back pain that didn't respond to more than 6 weeks of conservative therapy. We excluded those patients who had apophyseal ring fracture, sequestrate fragments, chronic discogenic back pain and severe neurological deficits. In those cases, we usually performed open discectomy. In cases with spinal instability, spinal fusion was considered the first option. Using these indications, appropriate decompression was achieved with PELD for all patients except one in the present study. Regarding the prognostic factors for PELD, Ahn et al. have analyzed 43 consecutive adult patients who underwent PELD for recurrent disc herniation (20). They showed that a better outcome was obtained for the patients who were younger than 40 years, the patients with a duration of symptoms less than 3 months and the patients who were without concurrent lateral recess stenosis. We believe the good surgical outcomes that were achieved in the present study are also attributable to the young age of the patients. Adolescents with lumbar disc herniation usually do not have severe degenerative changes such as lateral recess stenosis. Therefore, obtaining appropriate decompression is usually possible with PELD, which resulted in the successful outcome of this present study.

After conventional discectomy, a significant number of patients suffer from residual back pain (7, 12–15). Postoperative degenerative changes such as gradual disc space subsidence and facet joint degeneration could explain this negative outcome (12, 20). Unlike open discectomy, the posterior paraspinal structures are preserved during PELD. Furthermore, only the targeted removal of the herniated fragment is usually performed during PELD. Therefore, in the beginning of this study, we assumed that PELD might show a better result than open discectomy in terms of postoperative back pain. In the present study, the mean VAS scores of back pain were significantly decreased after PELD at a mean follow-up of 37.2 months (from 7.74 ±2.38 to 1.89 ±1.74, respectively). However, all 4 of the patients (8.7%) who showed fair outcomes still suffered from moderate back pain (mean VAS score: 5.8; range: 5–7), although one of them underwent subsequent open discectomy. Therefore, we cannot definitely say that PELD is superior to open discectomy in regard to postoperative back pain. Further long-term follow-up evaluation is warranted to elucidate the effect of PELD on postoperative back pain.

The most frequent complication of PELD in this study was temporary dysesthesia, and this was probably the result of thermal or mechanical irritation of the traversing root or the dorsal root ganglion (29). Temporary dysesthesia has been reported to develop in up to 20% of the patients undergoing PELD (24, 29). Sympathetic mediated pain, causalgia, quadriceps atrophy, psoas muscle hematoma and wound infections are other complications reported after PELD (24, 29, 37). Recently, the postoperative complications of PELD have been decreasing as a result of advances in minimally invasive surgical techniques. Ahn et al. have reported transient dysesthesia in 4.7% of their patients (20). In this series, only one patient (2.2%) showed transient dysesthesia. Because PELD is performed via the posterolateral transforaminal route, the precise identification of a safe "triangular working zone" during the procedure is of utmost importance to avoid complications (24). In this study, we always took an epidurogram to identify the location of both the traversing root and the dorsal root ganglion. We then carefully checked as to whether the patient felt severe leg pain or not during each step of the procedure.

Conclusions

In selected cases, performing PELD for adolescent soft lumbar disc herniation shows a high success rate comparable to success rates for open discectomy or chemonucleolysis. We believe that PELD is a good treatment option for adolescent soft lumbar disc herniations.

Acknowledgment

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Benign Splenic Epithelial Cyst Accompanied by Elevated Ca 19-9 Level:

A Case Report

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Abstract

We report the case of a 30-year-old woman with a benign epidermoid splenic cyst and a high CA 19-9 serum level (268 U/mL). The patient underwent resection of the cyst and splenectomy. After removal of the cyst, the serum CA 19-9 level decreased to a normal level within 6 weeks. True non-parasitic splenic cysts are rare. Approximately 30 cases of benign true splenic cysts with a high CA 19-9 serum level have been published.

Key Words: Splenic epidermoid cyst, CA 19-9.

Introduction

CYSTIC CHANGES OF THE SPLEEN are very rare. Based on the presence or absence of cellular lining of the cystic wall, splenic cysts are classified as primary (true) or secondary (pseudo)cysts (1, 2). Primary splenic cysts other than those of hydatid disease, which is endemic in Turkey, are also very uncommon. So far, elevated carbohydrate antigen 19-9 (CA 19-9) serum levels accompanying splenic cysts have been reported in approximately 30 cases, of which most were of epithelial origin (3–20).

In this paper we report an additional patient with cystic lesion of the spleen in the left upper quadrant, accompanied by increased serum CA 19-9 level.

Case

A 30-year-old female patient with left upper quadrant and left shoulder pain, and mass in the left hypochondrium, was admitted to our hospital. The patient's medical history was unremarkable, and she denied any trauma.

On physical examination, a palpable mass was found in the left upper quadrant. Laboratory data were normal except for high CA 19-9 serum level (268 U/mL; normal: 0–27 U/mL). The level of other tumor markers, such as CEA and CA 125, was also normal. Serologic tests were negative for hydatid disease. Abdominal ultrasound and computed tomography revealed a splenic cyst 10 cm in diameter; the cyst was apparently in direct contact with the stomach, spleen, and pancreas. No other intra-abdominal abnormality was found (Fig. 1).

Exploratory laparotomy confirmed a centrally located splenic cyst 10 cm in diameter. No other pathology was detected. Splenectomy was per-

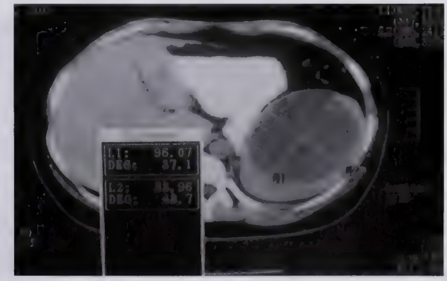

Fig. 1. CT scan showing a large and centrally located splenic cyst.

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formed, since conservative treatment is not possible when the spleen is almost totally occupied by the cyst (Figs. 2A and B). The histopathological diagnosis was an epithelial splenic cyst (Fig. 3). The postoperative course was uneventful and the patient was discharged on the third postoperative day. CA 19-9 serum level returned to normal (8.9 U/mL) six weeks later. The patient was doing well, with normal CA19-9 levels, during a follow-up period of 30 months.

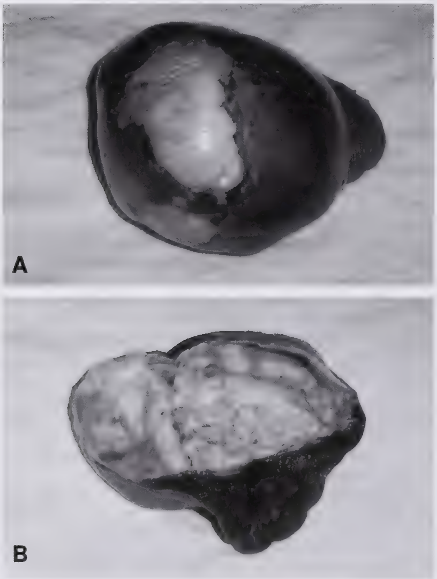

Fig. 2. **(A)** Macroscopic view of the splenic cyst. **(B)** Inside of the cyst.

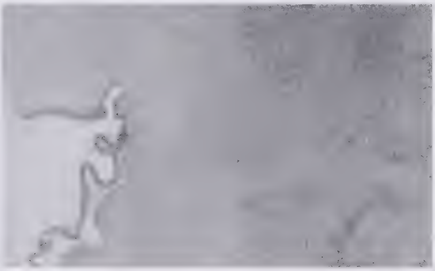

Fig. 3. Hematoxylin-eosin stain of a section of the cyst wall showing epithelial cellular lining (H&E × 40).

Discussion

Splenic cysts may be primary (true) or secondary (pseudocyst), depending on the presence or absence of an inner cellular lining (1, 2). Most true splenic cysts are epithelial in origin and have embryonic inclusion of epithelial cells from adjacent structures (6, 11, 21).

Although CA 19-9 is a reliable marker for pancreatic adenocarcinoma, both normal and tumoral human epithelial cells may produce it. High serum levels of CA 19-9 may accompany benign gastrointestinal diseases such as liver cirrhosis, acute cholangitis, obstructive jaundice and benign pancreatic conditions (6, 22, 23).

The first case of a splenic cyst with elevated serum CA 19-9 was reported by Terada et al. (20) in 1994. Since then, elevated CA 19-9 serum levels have been reported in approximately 30 cases of splenic cysts, most of them of epithelial origin (4–20).

Splenic epithelial cysts occur predominantly in children and young women (13). Small cysts are usually asymptomatic. The initial symptoms and signs referable to large cysts may include vague abdominal pain and a palpable mass in the left upper quadrant with or without symptoms due to compression of adjacent organs (10, 24).

Surgery is the only treatment for a splenic cyst with increased CA 19-9 level. In addition to conventional splenectomy, laparoscopic splenectomy and excision of the cyst and conserving spleen have been reported as alternative methods (13, 15).

Conclusion

Complete removal of the cyst by open or laparoscopic surgery is mandatory to ensure entire extirpation of cancer antigen-producing epithelium (6). Epithelial lining of true splenic cyst may be demonstrated by immunohistochemical analysis to produce this cancer antigen. Following removal of the cyst, serum levels of tumor markers should normalize (6, 20).

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Surgical Management of Functional Tricuspid Regurgitation with a New Remodeling Annuloplasty Ring

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Abstract

Background: Moderate-to-severe functional tricuspid regurgitation (TR) should be corrected in patients undergoing surgery for left-sided valvular diseases, to improve long-term outcomes. Several techniques of surgical repair (suture annuloplasty or prosthetic annuloplasty) to correct this condition have been described. Multiple clinical studies have shown the superiority of prosthetic remodeling annuloplasty over the other surgical approaches. Despite this, suture-based annuloplasty remains the most commonly used technique for tricuspid valve repair. A new 3-dimensional remodeling prosthesis has been developed to address the issue of residual TR. We report our early experience with this new 3-dimensional prosthetic remodeling ring, the Edwards MC3 system.

Material: From August 2002 to March 2004, 51 patients (24 male, 27 female, mean age 64±15, ejection fraction 49±15, median NYHA III [II–IV]) underwent tricuspid valve repair for functional TR due to annular dilatation, with the Edwards MC3 system. Etiology of left-sided valvular disease was: rheumatic (n=19), degenerative (n=16), ischemic cardiomyopathy (n=1), and endocarditis (n=5). Twenty (50%) patients underwent redo operations. Concomitant procedures included: mitral valve surgery (repair n=34, replacement n=14), aortic valve replacement (n=5), coronary artery bypass graft (n=8) and left arterial maze (n=16). Median EuroSCORE was 12% (1 – 74%) in this patient population.

Results: Operative and late mortality were 3.8% (n=2) and 13.7% (n=7), respectively. Echocardiography at discharge showed a mean TR decrease from 3.1±0.9 to 0.3±0.4 ($p<0.001$) and mean mitral regurgitation (MR) decrease from 3.2±1 to 0.1±0.1 ($p<0.001$), while ejection fraction increased to 53% ($p=0.047$), and at 6-month follow-up, mean TR and MR remained unchanged.

Conclusion: Concomitant tricuspid valve repair for functional TR with left-sided valve surgery carries a low operative mortality. The Edwards MC3 annuloplasty system is relatively simple to implant and corrects TR effectively (without significant residual TR), while providing excellent short-term clinical results. The 3-dimensional saddle shape of this ring may further optimize the fixation of the annulus in systolic position, and improve long-term results. Larger clinical series with longer-term follow-up are necessary to confirm these early promising results.

Key Words: Tricuspid regurgitation, surgery, valve repair, remodeling, annuloplasty.

Introduction

TRICUSPID REGURGITATION is a common finding in patients with severe mitral valve regurgitation. The severity of this condition often increases in the presence of pulmonary hypertension and/or left ventricular dysfunction (1). This so-called functional TR is due to annular dilatation (Carpentier's Type I dysfunction) (2). Previous anatomical studies have shown that annular dilatation does not affect the different segments of the tricuspid annulus equally (3). The diameter of the anterior segment of the annulus can increase up to 40%, whereas its posterior segment can dilate up to 80% of its initial diameter (3). The dilatation of the septal segment is limited (maximum 10%) because of its close anatomical relationship with the fibrous skeleton of the heart. Several techniques of surgical repair (suture annuloplasty or prosthetic annuloplasty) to correct this condition have been described (4, 5). Multiple clinical studies have demonstrated the superiority of remodeling annuloplasty over other repair procedures (2, 6, 7). In 2002, a new generation of annuloplasty rings was introduced by Edwards-Lifesciences (Edwards MC3 annuloplasty system, Edwards LLC, Irvine, CA). The main characteristic of this prosthetic ring is its 3-dimensional saddle shape, which perfectly fits the anatomical configuration of the tricuspid annulus. We report our early clinical experience with this new prosthetic device in patients undergoing cardiac surgery for functional TR and concomitant left-sided valve diseases.

Patients and Methods

A computer-based registry of all cardiac surgery patients at the Mount Sinai Medical Center was used to identify patients undergoing tricuspid valve surgery for functional TR between August 2002 and March 2004. In this period, 51 patients underwent tricuspid valve replacement (TVR) with the new Edwards MC3 annuloplasty system in ad-

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dition to left-sided valve surgery. Medical charts were reviewed for preoperative, intraoperative, and postoperative clinical variables. Follow-up information such as survival, clinical status and most recent echocardiography was obtained by contacting patients and/or referring physicians, and reviewing charts. Additional survival information was obtained using the social security death index. This research was done in accordance with our local institutional review board.

This patient population included 27 women (53%) and 24 men (47%). The mean age in this series was 64±15 years. Eighty-five percent (n=42) of the patients were in New York Heart Association (NYHA) functional class III and IV preoperatively. Mean left ventricular ejection fraction was 49±15%. Twenty patients (39%) underwent reoperative cardiac surgery. Eighteen patients (35%) were in atrial fibrillation and the remaining 33 patients (65%) were in sinus rhythm. Pulmonary hypertension, defined as a systolic pulmonary artery pressure greater than 45 mm Hg, was present in 32 patients (63%). Median expected mortality by EuroSCORE was 12% (1–74%) in this patient population. Preoperative characteristics of these patients are summarized in Table 1.

A trans-thoracic echocardiography (TTE), as well as right and left heart catheterization, was performed on all patients. The mechanism of TR was Carpentier's functional classification Type I (annular dilatation). The severity of TR, as assessed by Doppler echocardiography, was graded on a scale from 1+ to 4+ (1+ mild, 2+ moderate, 3+ moderate to severe, 4+ severe) (8). The results were as follows: forty-one patients (80%) had >3+ TR, eight (16%) had 2+ TR, and two (4%) had only 1+ TR. Mean TR grade was 3.2±0.9. Patients with 1+ and 2+ TR had a severe dilatation of the tricuspid annulus on the TTE (annular diameter greater than 40 mm). Etiology of left-sided valvular disease was: rheumatic (n=19), degenerative (n=16), ischemic cardiomyopathy (n=1), and endocarditis (n=5) (Table 2).

Intraoperative trans-esophageal echocardiography (TEE) was used for all patients. It was not used to assess the severity of TR, but played a crucial role in evaluating left ventricular function, quality of repair, and de-airing of the cardiac cavities at the end of the procedure.

Following a median sternotomy, cardiopulmonary bypass (CPB) was instituted between the ascending aorta and superior and inferior venae cavae with mild-to-moderate systemic hypothermia. Myocardial protection was achieved with antegrade and retrograde cold-blood, high-potassium cardioplegia. Left-sided valvular heart diseases were corrected first. The mitral valve was exposed through Sondergaard's groove. In patients with a history of atrial fibrillation, a modified left atrial maze procedure was performed by cryothermia (CryoCath Technology, Pointe-Claire, Canada) prior to the mitral valve procedure (n=16, 31%). Mitral valve repair was performed using Carpentier's techniques in 34 patients (66%), whereas replacement was done in 14 (27%). Other concomitant procedures included aortic valve replacement (n=5, 10%) and coronary artery bypass graft procedures (n=8, 16%) (Table 3).

A right atriotomy parallel to the atrio-ventricular groove was used to expose the tricuspid valve. Tricuspid valve analysis confirmed the presence of Type I dysfunction according to Carpentier's functional classification, with severe annular dilatation in all patients. Tricuspid valve (TV) repair was performed using the Edwards MC3 annuloplasty system. The prosthetic ring has a 3-dimensional shape, and is constructed of a titanium alloy with a

TABLE 1
Patient Demographics

Characteristics	n (%)
Female/male	27/24
Mean age (years)	64±15
NYHA class I	3 (6)
II	6 (12)
III	27 (53)
IV	15 (29)
Atrial fibrillation	18 (35)
Pulmonary HTN	32 (63)
Mean EF (%)	49±15
Reoperation	20 (40)

EF=ejection fraction, NYHA=New York Heart Association, HTN=hypertension.

TABLE 2
Intraoperative Mitral Valve Analysis: Valve Dysfunction According to Carpentier's Functional Classification and Etiology

Dysfunction Type	n (%)
Type I	9 (18)
Type II	10 (20)
Type IIIa	14 (27)
Type IIIb	17 (33)
Etiology	**n (%)**
Rheumatic	19 (37)
Degenerative	16 (32)
Ischemic cardiomyopathy	9 (18)
Dilated cardiomyopathy	1 (2)
Endocarditis	5 (10)

TABLE 3
Surgical Procedures

Procedure	n (%)
Tricuspid Valve Repair with MC3 Ring 51	
26 mm	17 (33)
28 mm	14 (27)
30 mm	7 (14)
> 32 mm	13 (26)
Concomitant Procedures	
MV repair	34 (66)
MVR	14 (27)
AVR	5 (10)
CABG	8 (16)
LA maze	16 (31)
Others	2 (3.9)

MV=mitral valve, MVR=MV regurgitation, AVR=aortic valve replacement, CABG=coronary artery bypass grafting, LA=left atrial.

sewing ring that consists of a layer of silicone rubber, covered with polyester velour cloth sewn with a single seam. Using the tricuspid valve sizer, the appropriate ring size was selected based on the distance between the antero-septal and postero-septal commissures, and the surface area of the anterior leaflet. For functional TR, based on the measured distance, the size of the ring was downsized by at least one size. Ring size implanted for TV repair varied from 26 – 34 mm: for 17 patients (33%) a 26-mm ring was used, for 14 (27%) a 28-mm ring, for 7 (14%) a 30-mm ring, and for 13 (26%) a 32-mm ring or larger. Ring implantation was performed without any complications, in all patients, in less than 20 minutes. The mean CPB time was 179±64 min and cross-clamp time 116±66 min.

Statistical Analysis

Values are expressed as the mean ± standard deviation, median (range) or as a percentage. Statistical significance was considered when a p value was less than 0.05. Comparison between groups was performed with use of analysis of variance, Student's test, or the chi-square test, as appropriate. The Kaplan-Meier method was used to determine the actuarial survival curve.

Results

Mortality and Morbidity

Operative mortality was 3.8% (n=2), cause of death being multi-organ system failure in both patients (Table 4). Postoperative morbidities were respiratory failure (requiring ventilation >72 h postoperatively) (n=1), low cardiac output requiring pharmacological support (n=1), and deep sternal infection (n=1). A permanent pacemaker insertion was necessary in 7 patients (13.7%), mainly due to sick sinus syndrome after maze procedure.

TABLE 4
Mortality and Morbidity

	n (%)
Mortality	2 (3.9)
Multi-organ system failure	2 (3.9)
Morbidity	3 (5.9)
Low cardiac output	1 (1.9)
Sternal infection	1 (1.9)
Respiratory failure	1 (1.9)

Follow-up

Patients and/or referring physicians were contacted by telephone for follow-up information and medical charts were reviewed. Median follow-up time was 523 days (range: 37 – 1004) and follow-up was 90% complete. Late mortality was 13.7% (n=7). The causes of death were gastrointestinal hemorrhage (n=1), systemic neoplasia (n=2), and unidentified (n=4). No valve-related complications (ring dehiscence, prosthetic endocarditis, or thrombo-embolic events) were documented during the follow-up period.

Echocardiographic Results

Tricuspid regurgitation was effectively reduced after this remodeling annuloplasty. At discharge, TTE showed a significant decrease of the mean TR from 3.1±0.9 to 0.3±0.4 ($p<0.001$) in all patients. Similarly, in patients who underwent mitral valve repair, mean MR decreased from 3.2±1 to 0.1±0.1 ($p<0.001$). No significant change in mean ejection factor was demonstrated (from 49±14 to 48±14%, p=ns). No patient had more than mild (>1+) TR after surgery.

At follow-up, 26/42 patients (62%) underwent repeat TTE. Mean TR and MR remained constant. All patients had mild (1+) or less TR at follow-up: none to trace = 11 (42%); mild (1+) = 15 (58%).

Discussion

Indications for Surgery

Tricuspid valve regurgitation has often been neglected in patients undergoing cardiac surgery for left-sided valvular heart disease. The main reason is that it was thought that TR decreases after surgical correction of left-sided lesions. However, the major issue is that the regression of TR is unpredictable after surgical treatment of mitral and/or aortic valve diseases. Left untreated, a significant number of patients will develop severe symptomatic TR over time. The persistence or the worsening of this condition correlates with an increased morbidity and mortality, mainly due to congestive heart failure, demonstrating the limitations of current medical therapy. In addition, most of these patients are not offered a second operation, because tricuspid valve re-operation for severe TR is associated with a high operative mortality (9, 10). Furthermore, in a recent study, Nath et al. have demonstrated that even moderate tricuspid regurgitation negatively impacts survival, regardless of left ventricular function or pulmonary artery pressures (Fig. 1; 1). This better understanding of the negative impact of functional TR on survival has several clinical implications.

The presence of TR and its severity should be evaluated carefully in patients undergoing mitral and/or aortic valve surgery. Since the severity of regurgitation depends upon multiple hemodynamic variables (preload, afterload, and right ventricular contractility), preoperative TTE is the best diagnostic tool to determine the presence and severity of this condition. The use of intraoperative TEE to determine the presence of TR should be avoided because general anesthesia induces a systemic vasodilatation, resulting in a significant afterload reduction that may lead to underestimation of TR severity (11).

This has led to more frequent surgical correction of functional TR at the time of initial operation for mitral and/or aortic valve disease. Currently, it is well accepted that all patients with TR greater than 2+ should undergo concomitant tricuspid valve repair in combination with other surgical procedures. The surgical indication for patients with TR equal to or less than 2+, however, remains controversial. In these patients the severity of the annular dilatation is another important variable that should be taken into consideration. In a recent study, Dreyfus et al. suggested that annular dilatation might be a more suitable indicator for tricuspid valve repair than the degree of TR (12). In this study, 311 patients were divided into two groups according to the severity of annular dilatation (upon intraoperative inspection). In group 2 (n=148 [47.6%]) patients underwent mitral valve repair with a concomitant tricuspid valve annuloplasty (annular diameter >70 mm), whereas in group 1 (n=163 [52.4%]) the tricuspid valve was not repaired (annular diameter <70 mm). The severity of TR was similar in both groups according to preoperative echocardiography (Group 1: 0.7±0.5 vs. Group 2: 0.9±0.6). After a mean follow-up of 4.8 years, TR increased by more than two grades in 48% of the patients in group 1 and in only 2% of the patients in group 2 (p<0.001). The authors concluded that tricuspid annular dilatation is an ongoing process that will lead to severe TR over time and warrants surgical correction regardless of the severity of TR.

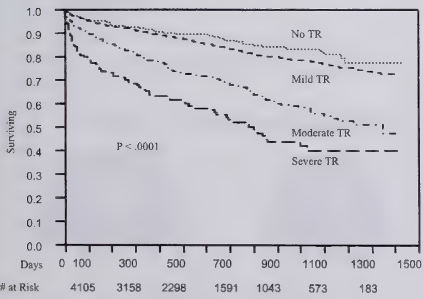

Fig. 1. Kaplan-Meier survival curves for all patients with tricuspid regurgitation (TR). Survival rate was significantly lower for patients with moderate and severe TR. (Reproduced with permission from Nath et al. [1].)

Our group, in collaboration with Professor A. Carpentier, has developed and implemented the following algorithm for surgical decision making in the management of patients with TR equal to or less than 2+, based on the severity of annular dilatation (Fig. 2). In this setting we recommend inspection of the tricuspid valve. If organic lesions are present, they should be addressed and treated using Carpentier's standard repair techniques. If the patient presents with only functional TR, an appropriate valve sizer is used to measure the surface of the anterior leaflet. After appropriate selection of the ring, which also indicates the optimal shape and size of the annulus, the degree of annular dilatation is assessed using a sizer one size larger. If the sizer covers the orifice area, this indicates the presence of mild-to-moderate annular dilatation. In this case it is likely that after the correction of left-sided lesions, TR will improve, so this condition may be considered reversible. Therefore, a conservative approach without tricuspid annuloplasty seems justified. In the presence of severe annular dilatation (if the larger sizer does not cover the orifice area) it is unlikely that the annular dilatation and TR will recede completely after correction of the left-sided lesions. In this scenario, a remodeling annuloplasty to correct TR

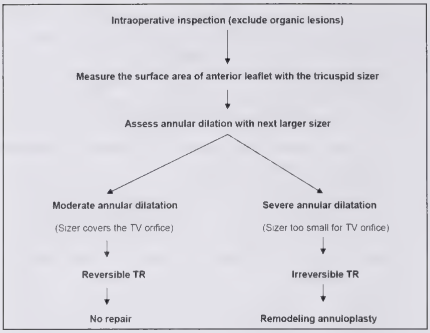
Intraoperative inspection (exclude organic lesions)
Measure the surface area of anterior leaflet with the tricuspid sizer
Assess annular dilation with next larger sizer
Moderate annular dilatation
(Sizer covers the TV orifice)
Reversible TR
No repair
Severe annular dilatation
(Sizer too small for TV orifice)
Irreversible TR
Remodeling annuloplasty

Fig. 2. Decision making for patients with functional tricuspid regurgitation (TR) (< 2+).
TV = tricuspid valve.

is recommended. Pulmonary artery pressures and left ventricular function are other important variables that must be taken into consideration. In the presence of pulmonary hypertension and/or left ventricular dysfunction, we have a lower threshold to perform tricuspid valve annuloplasty in patients with mild TR. This algorithm is summarized in Fig. 2.

Operative Techniques

During the last four decades, several repair techniques have been described for the surgical correction of functional TR with severe annular dilatation. The initial repair techniques were palliative; their goal was to reduce the diameter of the annulus by plication or circumferential constriction (Fig. 3A). The Kay suture annuloplasty consisted of the placement of multiple sutures around the posterior segment of the annulus where the dilatation is maximal. The procedure not only significantly reduced the orifice area by eliminating the posterior segment of the annulus, but also transformed the tricuspid valve into a bicuspid structure. However, this technique was associated with multiple drawbacks, including the fibrotic transformation of the posterior leaflet, and continued dilatation of the anterior segment of the annulus. The long-term results were not satisfactory and it was abandoned. The other suture annuloplasty technique (De Vega repair) consists of the placement of two semicircular pursestring sutures from the antero-septal commissure to the postero-septal commissure, to achieve an annular narrowing. This technique produces a semicircular deformation of the tricuspid orifice and, for purely geometric reasons, causes relative invagination of the leaflets, impairing their motion. Further dilatation of the tricuspid orifice due to migration of the suture is common and is at the origin of recurrent TR (6, 7; Fig. 3A).

In the early 1970s, Carpentier introduced the concept of remodeling annuloplasty for the correction of TR. Prosthetic rings of a suitable size are selected, based on the distance between the antero-septal and the postero-septal commissures as well as the surface area of the anterior leaflet. The remodeling annuloplasty restores the normal shape of the annulus and thereby allows both a normal orifice area and normal valve function (Fig. 3B). The goal of reconstructive valve surgery is to preserve leaflet mobility and to create a large surface

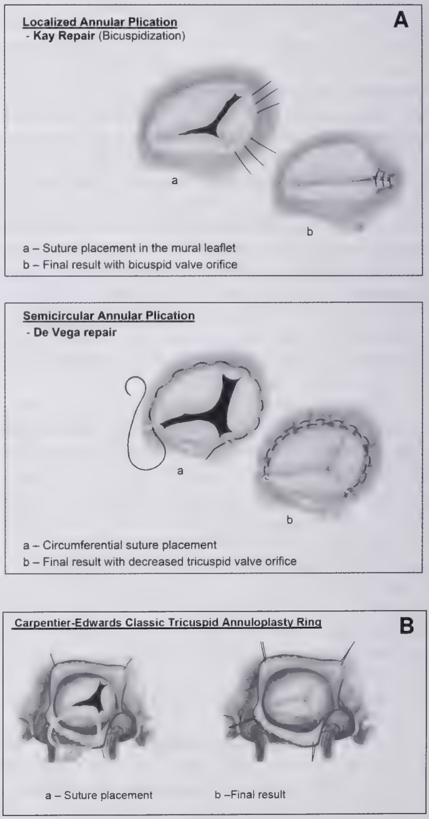
Localized Annular Plication
- Kay Repair (Bicuspidization)
A
a
b
a – Suture placement in the mural leaflet
b – Final result with bicuspid valve orifice
Semicircular Annular Plication
- De Vega repair
a
b
a – Circumferential suture placement
b – Final result with decreased tricuspid valve orifice
Carpentier-Edwards Classic Tricuspid Annuloplasty Ring
B
a – Suture placement
b –Final result

Fig. 3. **(A)** Tricuspid valve annuloplasty techniques: suture-based procedures. **(B)** Tricuspid valve annuloplasty technique: remodeling annuloplasty.

of coaptation, while preventing further annular dilatation (2). From a design perspective, the prosthesis has a 2-dimensional shape and is semi-rigid. The ring should be manually bent to fit the 3-dimensional saddle shape of the tricuspid annulus, which is more superficial in the anterior area due to aortic bulging and deeper in the septal area (Fig. 3B). Several clinical studies have demonstrated the superiority of the remodeling annuloplasty over suture-based techniques in terms of freedom from TR and reoperation (2, 6, 7, 13). Despite these excellent results, it has been suggested that this mismatch in configuration between the prosthetic ring and the tricuspid annulus has been at the origin of incidental reports of ring dehiscence. In 2002, a new generation of prosthetic rings was introduced. The Edwards MC3 ring system has adopted the concept of the remodeling annuloplasty. This ring has a 3-dimensional design and is preconfigured to best accommodate the saddle shape of the annulus. As demonstrated in our series, the implantation of this ring was relatively simple and provided excellent early clinical and echocardiographic results. This 3-dimensional configuration may offer a potential advantage with respect to increased stabilization of the annulus. However, the durability of this repair must be assessed with long-term studies, especially those comparing this prosthesis to the current standard, the classical Carpentier Edwards tricuspid ring.

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Rapid Ventricular Pacing due to Electrocautery:

A Case Report and Review

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Abstract

It is well known that the use of electrocautery during surgery can interfere with the functioning of pacemakers. The most common problem is that the electrocautery is interpreted by the pacemaker as cardiac electrical activity, which inhibits the pacemaker from firing, leading to bradycardia. The use of electrocautery in a site remote from the pacemaker generator normally does not cause interference. It is also very unusual to develop a tachycardic response to the electrocautery. We report a case of electrocautery causing rapid pacing during transurethral resection of bladder polyps. The possible causes of inappropriate rapid pacing are reviewed.

Key Words: Pacemakers, tachycardia, electrocautery, electromagnetic interference.

Introduction

ALMOST ALL ELECTRONIC DEVICES can be affected by external electromagnetic interference (EMI). Attempts to lessen the effects of EMI upon pacemakers have included metallic shielding to protect against high frequency EMI; noise sampling periods, which convert pacemakers to a fixed rate if continuing EMI is sensed; and bipolar leads, which have improved the rejection of noise over the original unipolar lead (1). Yet these improvements in pacemaker design, helpful as they may be, must be continuously reevaluated (2). This is evidenced by reports of mobile phones and cardiac monitors interfering with pacemaker functioning (3–5). This paper reports an inappropriate intraoperative rate response of a ventricular sensed and paced minute ventilation rate adaptive (VVIR) pacemaker to electrocauterization remote from the chest wall.

Case

An 83-year-old, 63 kg male presented for cystoscopic transurethral removal of bladder polyps. The pertinent medical history and preoperative testing included amyloid cardiomyopathy, chronic congestive heart failure, coronary artery bypass atrial fibrillation necessitating pacemaker placement, benign prostate hypertrophy, normal electrolytes, and a normal preoperative roentogram showing intact pacemaker leads. Preoperative evaluation indicated that the patient had a bipolar VVIR minute ventilation rate responsive Tempo™ VR, model 1102 pacemaker (Telectronic Pacing Systems, Englewood, CO) with a fixed rate of 60 beats per minute (bpm), a maximum rate of 100 bpm, a magnet rate of 100 bpm, complete and normal capture of the pacemaker with and without a magnet, and satisfactory sensing. The EKG showed a ventricular paced rhythm, at a rate of 60 bpm.

Intraoperatively, the patient was monitored with continuous electrocardiography, non-invasive blood pressure measurements, pulse oximetry, and capnography via nasal cannula. The capnogram was used to determine the respiratory rate. The patient's resting vital signs were stable at a paced heart rate of 60 bpm, blood pressure of 120/85 mm

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Hg with a mean of 98 mm Hg, and oxygen saturation >99% with a fractional concentration of inspired oxygen (FiO_2) of 0.26. Anesthesia consisted of a spinal anesthetic at the 10th thoracic vertebra.

Throughout surgery there were ECG changes ranging from a paced rate of 60 bpm when the electrocautery was not in use to a paced rate of 100 bpm when it was in use (Figs. 1 and 2). The patient's vital signs remained stable at both paced rates, with a mean arterial pressure of 70–80 mm Hg and an unchanged respiratory rate. The patient did not complain of angina or dyspnea during the surgery. In an attempt to attenuate the EMI from the electrocautery, the dispersion pad was placed on the right lower extremity and bipolar electrocautery was used in short bursts. Despite these recommended maneuvers, the electrocautery continued to cause inappropriate pacemaker rate response. Nonetheless, the surgery was completed without complication and the postoperative course was uneventful.

Discussion

To the best of our knowledge, this is only the second case reported in which a pacemaker responded to electrocautery with tachycardia, during transurethral resection surgery. Given that postoperative evaluation of the pacemaker by a compatible programmer did not detect a malfunction, interpretation of intraoperative events focused upon inappropriate rate response to EMI by a normal functioning pacemaker. Normally, titanium casing, filter circuitry, and programming shield pacemakers from the effects of EMI. But these shields are not infallible (6–9). Inappropriate pacing has been reported when the pacemaker has been placed in the active-programmable mode by a magnet, when an R wave is sensed in the noise response period, and when there is an incorrectly sensed increase in metabolic demand. Each of these reported causes of inappropriate pacing will be explored as possible explanations of the presented case.

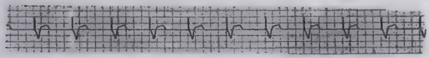

Fig. 1. Rhythm strip of ECG, when electrocautery was not in use.

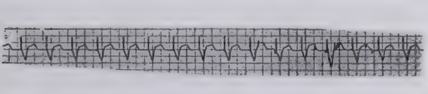

Fig. 2. Rhythm strip of ECG, while electrocautery was in use.

Manual programming is a normal function of modern pacemakers. It allows individualization of the pacemaker to the patient's metabolic needs. A programming wand, equipped with a magnet for pacemaker models that require it, places the pacemaker receiver into the active-programmable position. In this position, the pacemaker is programmable. The magnet, commonly used to place pacemakers in the fixed rate when EMI causes inappropriate inhibition of the pacemaker, paradoxically facilitates random reprogramming by EMI in pacemakers, which require it for programming. This is one way in which an inappropriate rate response may occur in a well-functioning pacemaker. An extensive list of pacemakers susceptible to random reprogramming in the presence of a magnet can be found in Domino and Smith. (6). The Telectronic 1102 model is not such a pacemaker.

Another possible explanation for the described intraoperative events in this case is the sensing of an R wave during the noise sampling period (NSP). The noise sampling period is best understood as it relates to the other components of the pacemaker timing-cycle. The timing-cycle is the time interval between a sensed beat and a paced beat or two paced beats. The timing-cycle is composed of three periods: the ventricular resettable refractory period (VRRP), the NSP, and the alert period. An R wave sensed in the VRRP will have no effect upon the timing-cycle because it is in the refractory period. An R wave sensed in the NSP will extend the NSP by a preset refractory period (RF). If an R wave is sensed in the alert period, the current timing-cycle will end, and a new one will be initiated. This design has been included in most modern pacemakers. Its purpose is to prevent EMI from causing prolonged pacemaker inhibition. The Telectronic 1102 timing-cycle is one of the simpler designs, in that the NSP is equal to the VRRP.

A report by Falkoff et al. described a predictable tachycardia in a paced patient with underlying atrial fibrillation (7). In this report, reproducible intermittent reversion to fixed-rate pacing during atrial fibrillation was recorded. During episodes of atrial fibrillation, an initial sensed beat established the VRRP; a second beat occurred in the NSP, causing reversion to the fixed rate; a third beat occurred in the alert period but was unsensed, because the pacemaker was in the fixed rate mode; and finally, a paced beat occurred in concordance with the fixed rate timing cycle. Although the patient in our case had an underlying atrial fibrillation, there were no observed conducted beats. If EMI generated by the electrocautery had mimicked an R wave or entire QRS complex, pacemaker inhibition rather than upper rate pacing at 100 bpm would have resulted; some observable conformational difference between the paced and EMI-generated QRS complexes would be expected; and the pulse-oximeter would have been interrupted by episodic pulseless electrical activity during electrocautery use. None of these occurred, suggesting a different mechanism.

The most likely explanation of the inappropriate rate response observed in our case involves the mechanism by which rate adaptive pacemakers link changes in metabolic demand to changes in pacing rate. Rate adaptive pacemakers attempt to match cardiac output to oxygen demand. This is accomplished by directly changing the pacing rate with the metabolic rate. In minute ventilation-sensing pacemakers, pacemaker leads detect changes in thoracic impedance. If the change is of a certain amplitude, the respiratory sensor of the pacemaker is triggered. The number of times that the respiratory sensor is triggered in a set time interval becomes the respiratory rate. Each change in respiratory rate results in a preset change in paced rate. The direct relationship between a change in respiratory rate and paced rate is the respiratory factor. In this case, the electrocautery probably caused a change in thoracic impedance, which led to a paced rate. The interpretation by a pacemaker of a change in thoracic impedance of respiration has been reported to cause inappropriate rate response. Reports have pointed to cardiothoracic surgery or vigorous upper limb movement (8, 9). Van Hemel et al. reported a serious complication in which an electrocautery was used to open the chest (9). Tachycardia of 150 bpm was observed during each use of the electrocautery. External heart massage was required until normal pacemaker function resumed. Upon opening the pericardium and using the electrocautery again, the surgeon noted a recurrence of the tachycardia. The tachycardia was refractory to internal defibrillation. Fortunately, the surgical and anesthesia teams were prepared for extracorporeal circulation. The observed wide complex tachycardia may not have been ventricular fibrillation, but rather pacemaker-generated QRS complexes. If so, the upper rate pacing would have been a normally response to the change in thoracic impedance generated by the electrocautery. Subsequent pacemaker evaluation revealed a normally functioning pacemaker.

In one previous report, electrocautery during transurethral resection of prostate surgery resulted in a paced rate of 130 bpm (10). This case report also involved a Telectronic (Telectronic Pacing Systems, Englewood, CO) VVIR pacemaker. The authors proposed that the electrocautery caused a change in thoracic impedance, which resulted in an increase in the pacemaker rate. We had a similar experience, and agree with their conclusion and their recommendations that preoperatively either these pacemakers should be reprogrammed out of the rate-responsive mode or else that the maximum pacing rate should be set to a rate that can be tolerated by the patient.

There are several maneuvers that can be done when intraoperative EMI interferes with pacemaker function: increasing the distance between the pacemaker generator and patient return electrode, using bipolar electrocautery in short random bursts, and resetting the pacemaker to ventricular paced and sensed mode with inhibition (VVI) are a few. The best approach is to first understand pacemaker function. Atlee and Bernstein have presented a protocol for management of the paced patient presenting for non-cardiac surgery (11). Briefly, the protocol suggests that the patient be seen by the pacemaker clinic prior to surgery, with a plan to reprogram the pacemaker, depending on the site of surgery and the equipment to be used, such as electrocautery. The response to a magnet should be determined. If the patient is pacemaker dependent, the pacemaker should be placed in the triggered or asynchronous mode. In the event of hemodynamic instability, the anesthesiologist should be ready to place a magnet over the pacemaker generator, if appropriate, or establish external pacing. The location of the generator should be known, so that defibrillation pads are positioned at least 10 cm away from the generator to avoid pacemaker damage. And finally, if the pacemaker is to be interrogated in the postoperative care unit, arrangements should be made pre- or intra-operatively.

In our case, placing a magnet over the generator would have switched the pacemaker to a fixed rate, and eliminated the rate responsive feature. Since the use of electrocautery was limited to brief applications, and the patient tolerated the faster rate, this was not done. Conversion to a fixed rate has the potential for R or T phenomenon, causing arrhythmias, competition of the pacemaker with the patient's native heartbeat, and phantom reprogramming. In retrospect, the best approach would have been to reprogram the pacemaker preoperatively, to disable the rate responsive feature. However, it was not anticipated that there would be electromagnetic interference.

A practice advisory for the perioperative management of patients with cardiac rhythm management devices was recently authored by an American Society of Anesthesiologists (ASA) Task Force (12). The guidelines include keeping the electrical field of the cautery away from the pacemaker generator, using short bursts of electrocautery, and using bipolar electrocautery if possible.

If electromagnetic interference is anticipated, the task force recommended that it be determined preoperatively whether the pacemaker should be reprogrammed to an asynchronous mode, or the rate adaptive functions should be suspended. According to the report, the ASA members were equivocal on both of these possible courses of action.

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Late Recurrent Pulmonary Typical Carcinoid Tumor:

Case Report and Review of the Literature

Ari Ciment, M.D.[1], Joan Gil, M.D., Ph.D.[2], and Alvin Teirstein, M.D.[3]

Abstract

Carcinoid tumors are uncommon pulmonary neoplasms. They are classified histologically as either atypical or typical. Atypical carcinoids are aggressive malignancies that require radical surgical resection and have a guarded prognosis with a propensity to metastasize and recur. Typical carcinoids are low-grade malignancies with relatively less metastatic or recurring potential and are usually treated with simple excision. Recurrence of a typical pulmonary carcinoid tumor more than a decade after initial resection is very rare. A patient with recurrence of a typical carcinoid tumor 11 years after resection of the primary lesion with one involved lymph node is reported here. Late recurrences are rare in both atypical and typical varieties, but are much more common in atypical carcinoids. The patient reported here represents the fifth case of recurrence of a typical carcinoid tumor more than ten years after resection. This suggests that, after resection of a typical carcinoid neoplasm, patients should be monitored carefully, especially if lymph node metastases are present at the time of surgery.

Key Words: Carcinoid, typical, atypical, recurrence, metastases, monitoring.

Late Recurrent Pulmonary Typical Carcinoid Tumor

PULMONARY CARCINOID TUMORS represent 2% of all primary lung neoplasms. They are usually classified as either atypical or typical. Most authorities agree that atypical carcinoids are malignancies that are treated as carcinomas with radical surgery (1). They have a guarded prognosis with a propensity to recur and metastasize. The typical variety has been regarded as a low-grade malignancy with less metastatic or recurring potential and is treated with simple excision. Recurrence of a typical pulmonary carcinoid tumor more than a decade after initial resection is rare. The following is a report of a patient who had a rare late recurrence of a typical carcinoid tumor 11 years after complete primary resection. This represents one of the latest known recurrences after surgery.

Case Report

In October 2004, an 80-year-old male presented with a one-month history of right-sided chest discomfort. Although a nonproductive cough had been present for many years, he denied wheezing, orthopnea, anorexia, weight loss, fever, chills or hemoptysis. In 1993, he had undergone a right lower lobectomy for an endobronchial typical carcinoid tumor. One positive hilar lymph node had been found. The patient had stable angina pectoris and medication-controlled diabetes. He denied exposure to known toxic inhalants except for a brief smoking history 50 years previously. Physical examination was normal except for a well-healed right thoracotomy scar. Spirometry was consistent with slight obstructive dysfunction. Oxygen saturation was 95% while breathing room air. A CT scan of the patient's chest revealed a large packet of mediastinal lymph nodes involving the pretracheal and subcarinal areas, and measuring 5 × 5.8 cm (Fig. 1). Positron emission topography (PET) scan revealed adenopathy exhibiting a standardized uptake value (SUV) of 4.9 and 11.9, respectively. After a non-diagnostic bronchoscopic needle aspiration, cervical mediastinoscopy yielded lymph nodes with typical carcinoid tumor, histo-

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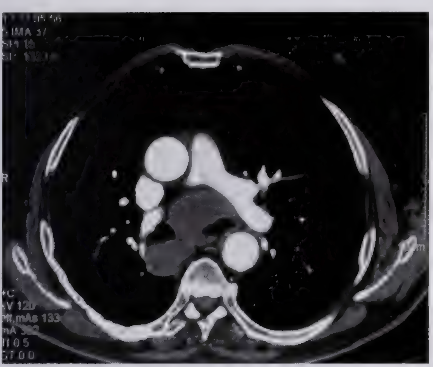

Fig 1. The CT scan of the chest revealed a large packet of mediastinal lymph nodes involving the pretracheal and subcarinal areas, and measuring 5 × 5.8 cm.

logically identical to the primary tumor resected 11 years previously.

Discussion

A majority of carcinoid tumors are located in the gastrointestinal tract, usually in the colon, rectum and small intestine. But 25% of them occur in the thorax, with two different clinical presentations:

1. An endobronchial lesion that causes hemoptysis, atelectasis and/or recurrent obstructive pneumonias.
2. A growing peripheral nodule, often discovered incidentally by a routine chest radiograph. CT examination often demonstrates vascular, circumscribed masses, which enhance with contrast. Though PET scanning is rarely positive in carcinoid tumors, there are reports demonstrating PET positivity, as in the patient reported here (2).

Carcinoid tumors are neuroendocrine malignancies arising from bronchial Kultchitsky cells, with less aggressive potential than large cell neuroendocrine carcinomas and small cell carcinomas. Histologically they consist of round cells with a recognizable nuclear chromatin pattern referred to as "salt and pepper," which frequently develops into an organoid pattern with a fine connective cell stroma and rich vascularization. By electron microscopy these tumors exhibit diagnostic neuroendocrine cytoplasmic "dense core" inclusions (3). Immunohistochemistry for standard neuroendocrine markers (neuron-specific enolase, chromogranin, synaptophysin) has been used by many to corroborate the histologic diagnosis (4). In 1972 Arrigoni et al. emphasized the entity of "atypical" carcinoid, a more aggressive form with biologic behavior and prognosis comparable to that of a carcinoma (5). Whether typical or atypical, these malignancies are characterized by small areas of necrosis, nuclear pleomorphism, absence of organoid or trabecular pattern, and areas of increased cellularity (Fig. 2). Currently, the sole diagnostic feature that distinguishes typical from atypical carcinoid is the number of mitoses. The diagnosis of typical carcinoid is supported only if the mitotic rate is equal to or lower than 2 mitoses/10 high power fields (HPF). The diagnosis of atypical carcinoid is established when there are 2–10 mitoses/HPF or in the presence of any necrosis. High mitotic rates above 10/10 HPF indicate a small cell carcinoma. Staining for the antigen Ki67 using the antibody MIB-1 has been used to determine the fraction of proliferating cells and to help ascertain the grade of the tumor (4).

Recurrence of carcinoid tumors after surgical resection varies between 2–9% and 5–30% for typical and atypical histologies, respectively. Froudarakis et al. found a statistical difference in survival between typical and atypical carcinoids. They noted no recurrences (6). Halevy et al. found no recurrences or distant metastases in 14 patients with bronchial adenomas after a 4–17 follow-up (7). One report of 95 patients who underwent lung resection revealed 10 recurrences. Seven of these had atypical histology. Lymph node metastases were more common in the atypical variety (8). Ferguson et al. analyzed 139 patients with resected pulmonary carcinoids (9). Recurrent carcinoid de-

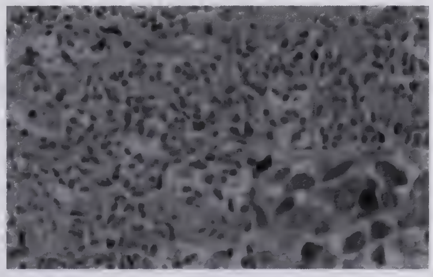

Fig. 2. The histological pattern of the mediastinoscopy biopsy specimen showed an organoid structure with characteristic rounded cells. These rounded cells (inset) demonstrated a "salt and pepper" pattern characterizing the fine intranuclear granular appearance of chromatin, consistent with the diagnosis of typical carcinoid tumor.

veloped in eight patients at postoperative intervals of 43±25 months. The authors concluded that the only significant predictor of recurrence is atypical histology, with a relative risk of recurrence of 7.9. Kaplan et al. noted a locoregional failure rate of 8.4% for typical carcinoids and 22.7% for atypical carcinoids (10). A study of 27 patients with atypical carcinoids showed a recurrence rate of 18.5% (11). Thomas et al. concluded that patients with atypical pulmonary carcinoid tumors with regional lymph node metastases have a high likelihood of developing recurrent disease if treated with surgical resection alone. Many of the atypical carcinoid patients (63.6%) developed systemic metastases at a median time of 17 months after diagnosis (12).

Recurrences more than ten years after lung resection, whether of the typical or atypical histological varieties, are uncommon. A 1978 case report detailed a case of recurrent carcinoid 32 years after initial resection (13). In all, there have been 4 reported typical carcinoid recurrences more than 12 years after surgical intervention. In a report of 82 cases, 65 "benign" and 17 "malignant," 1 of 2 recurrences in the typical group occurred 12 years after surgery (14). Another typical carcinoid occurred 16 years after primary resection in a group of 57 patients (15). A review of 60 patients with pulmonary carcinoids revealed that 1 out of 42 patients with typical carcinoid had recurrence 14 years after resection (16). And among 93 patients with typical carcinoid tumors, one had disseminated metastatic bone and liver disease 17 years after the resection. (17). These 4 cases, and the fifth reported here, highlight the rarity of recurrence and emphasize the need for close surveillance of resected typical carcinoids for many years after resection, especially if local lymph node involvement is present at the time of the original resection.

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Intestinal Tuberculosis and Secondary Liver Abscess

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Abstract

The incidence of intestinal tuberculosis (ITB) has been increasing in the West, due to the AIDS epidemic, transglobal immigration, IV drug abuse, an aging population, and an increase in the number of immunocompromised patients. Obstruction and perforation of the intestine are the most common and serious complications of ITB. Another complication, tuberculous liver abscess (TLA), is rare and usually associated with foci of infection in the lung or gastrointestinal tract. We report a case of a 17-year-old boy with Down syndrome who presented with multiple TLAs secondary to obstructive and multiple perforated ileal tuberculosis.

Key Words: Intestinal tuberculosis, tuberculous liver abscesses, surgical treatment.

Introduction

Abdominal tuberculosis (TB) is still a major problem in many regions of the world, especially in developing countries. And the incidence of ITB has been increasing in the West, due to the AIDS epidemic, transglobal immigration, IV drug abuse, an aging population, and an increase in the number of immunocompromised patients (1–3). In the abdomen, tuberculosis may affect the intestinal tract, lymph nodes, peritoneum and solid viscera (4). The lack of specific signs and symptoms of abdominal tuberculosis involving the peritoneum or intestinal tract frequently leads to missed or delayed diagnoses such as Crohn's disease, lymphoma, carcinoma, and periappendiceal abscess (5, 6). Obstruction, perforation, fistula formation, intestinal bleeding, traction diverticula and venous thrombosis are abdominal complications of ITB (7). Obstruction is the most common complication of ITB; it occurs in 12–60% of cases (7, 8). TLA is rare and usually associated with foci of infection in the lung or gastrointestinal tract (9). The bacilli reach the liver via the hepatic artery or the portal vein (10). Levine (11) classified hepatic tuberculosis as miliary tuberculosis, pulmonary tuberculosis with liver involvement, primary liver tuberculosis, tuberculoma, and tuberculous cholangitis.

We report a case of a 17-year-old boy patient with multiple TLAs secondary to obstructive and multiple perforated ileal tuberculosis.

Case Report

A 17-year-old boy with Down syndrome was admitted with a 6-week history of mild abdominal pain, fever, diarrhea, abdominal distension and 15 kg weight loss. The patient had been treated for ITB some 12 years earlier. On physical examination he was febrile (38°C) and tachycardic, and had a distended abdomen and a soft mass, about 10 cm diameter, in the middle abdomen. There were no signs of peritoneal irritation, and the liver, spleen and lymph nodes were not enlarged. Laboratory tests showed hypochromic anemia (hemoglobin 7.1 g/dL), normal white blood cells (8,000/mm^3), serum bilirubin 3.4 g/dL, alkaline phosphatase 340 IU, aspartate aminotransferase 42 U/L, alanine aminotransferase 59 U/L, high erythrocyte sedimentation rate (120 mm/h), and high

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CRP rate (15.9 mg/dL, upper limit 0.5 mg/dL). Chest x-ray showed no abnormalities, but CT scan of the abdomen showed irregular thickening of the small bowel and nonblocking mass in the abdomen (Fig. 1). The patient received metronidazole for diarrhea. After 5 days of follow-up he had acute abdominal and obstructive symptoms and his white blood count was 19,100/mm^3.

The patient had exploratory surgery, at which a mass in the middle abdomen was discovered. This mass consisted of a perforated ileum segment which was enclosed within the adjacent ileum segments. The perforated segment of the ileum was resected, and an end ileostomy was performed because of edema, dilatation and severe peritonitis. Although the patient appeared well on the first and second postoperative days, he began to have fever on postoperative day 3; on postoperative day 4 it reached 39°C. In searching for the source of the fever, blood, sputum, urine and stool cultures were taken and direct microscopies of urine, stool, and sputum were also examined. All of them were negative. We also took a chest radiogram, which was normal. Abdominal ultrasound (US) was done on postoperative day 6. It showed multiple cystic lesions, approximately 1 mm in diameter, in the liver. These were considered microabscesses. Abdominal magnetic resonance imaging (MRI) revealed multiple hypointense lesions diffusely spread in the liver (Fig. 2). Meanwhile, the pathological examination of the resected ileum revealed intestinal tuberculosis (Fig. 3).

We did a US-guided percutaneous aspiration of the cystic lesions for further diagnosis and discrimination between bacterial and tuberculous liver abscess. The aspirated material was cultured, underwent direct microscopic examination, and was sent for polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* DNA. Culture and microscopical examination were negative but PCR for *M. tuberculosis* DNA was positive. The lesions were diagnosed as tuberculous microabscesses, and an anti-TB treatment for both intestinal tuberculosis and tuberculous liver abscess was ordered. The treatment consisted of four drugs (isoniaside 300 mg orally daily, pyrasinamide 2,000 mg orally daily, ethambutol 1,500 mg orally daily, rifampicin 600 mg orally daily) for a two-month period and two drugs (isoniaside, rifampicin) for the rest of the therapy period (10 months). The patient was

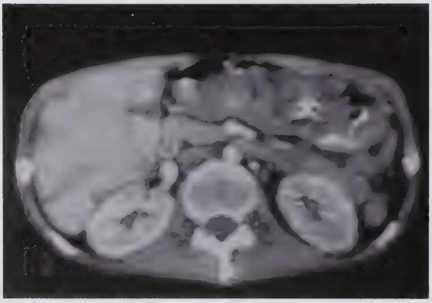

Fig 1. Contrast enhanced axial CT image through the upper abdomen shows concentric intestinal wall thickened and nodular, irregular infiltration of the omentum on the left epigastric region.

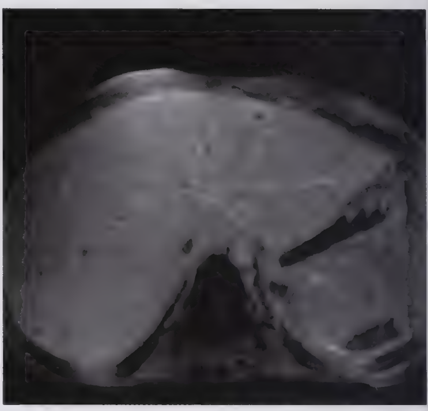

Fig 2. Post-contrast fat-saturation axial T1-weighted image through the upper abdomen shows well-defined, ring-contrast-enhanced, uniform multiple liver lesions.

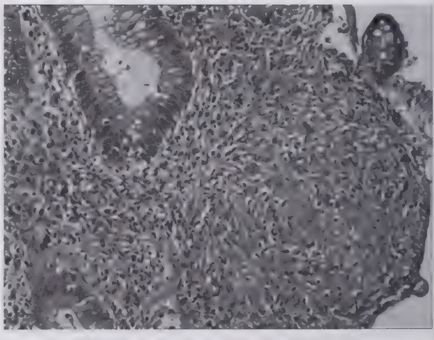

Fig 3. This section shows an intestinal mucosa and a granuloma; a round nodule with a large Langhans giant cell in the center surrounded by fibroblasts; and occasional lymphocytes.

discharged from hospital on postoperative day 15 without any other complications. The ileostomy was closed two months after the operation. An abdominal MRI was performed after the end of anti-TB therapy; there were no lesions visible on the liver (Fig. 4).

Discussion

TB can involve any part of the gastrointestinal tract, from mouth to anus, including the peritoneum and hepatopancreatobiliary system. ITB is predominantly a disease of young adults and the sex incidence is equal (12). Approximately 75% of patients with ITB have involvement of the distal small bowel and ileocecal region, possibly because of the increased physiological stasis, increased fluid and electrolyte absorption, minimal digestive activity and abundance of lymphoid tissue in this region (12–14).

It is often difficult to confirm the diagnosis of primary ITB, especially in emergency situations (15). Diagnosis of ITB is based on a comprehensive approach, including patient history as well as clinical lab tests and radiological findings (6). The most common symptoms of ITB are abdominal pain, diarrhea, weight loss, anorexia, fever, anemia, and lower gastrointestinal bleeding. Abdominal tenderness and distension and/or palpable abdominal mass are also relatively common physical findings (13–15). Many of these signs and symptoms were present in our patient.

Serum laboratory tests are usually nonspecific (15). Definitive diagnosis is essentially made by histology; Ziehl-Neelsen staining for acid-fast *bacilli* and culture can establish the diagnosis for up to 80% of the patients (16, 17). PCR of aspirated or biopsy specimens may facilitate diagnosis with higher sensitivity, and specificity and speed than routine culture, as in our case (15).

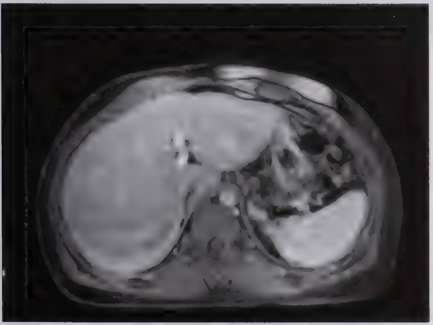
Fig 4. Post-contrast fat-saturation axial T1-weighted image through the upper abdomen appears normal.

While US and computed tomography (CT) show extramucosal changes directly, barium studies show mucosal pathology and complications (2, 18). CT also makes an important contribution in evaluating most of the complications of ITB, such as small bowel obstruction, perforation, and abscess formation (2).

The lack of specific signs and symptoms of abdominal tuberculosis involving the peritoneum or intestinal tract frequently leads to missed, delayed or erroneous diagnoses such as Crohn's disease, lymphoma, carcinoma, or periappendiceal abscess (5, 6).

Obstruction, perforation, fistula formation, intestinal bleeding, traction diverticula and venous thrombosis are reported complications of ITB (1, 7, 8, 13). Obstruction is the most common complication of ITB, occuring in 12–60 % of cases (7, 8). Though perforation is less common (1–15%) than obstruction, it is a serious complication (1, 7, 8). Multiple perforations are reported in 25–40% of cases (1, 8). Perforation can also be confined to a localized area, presumably due to the preexisting adhesive change, hypertrophied intestinal wall, and mesentery, as in our case (7, 8). The overall mortality of perforation has ranged from 25–45% (1).

Although most patients with ITB respond favorably to medical therapy, surgery should be considered for complications such as obstruction, free perforation, confined perforation with abscess, fistula and massive bleeding, or diagnostic uncertainty (1, 15, 19). The most effective surgical treatment of complicated ITB is resection, with 5 cm margins from macroscopically diseased tissue and end-to-end anastomosis. Simple closure of perforations is not recommended because of the high incidence of leak and fistula formation (1, 15). We did not perform end-to-end anastomosis because of edema, dilatation and severe peritonitis, and diagnostic uncertainty.

TLAs are rare and usually associated with foci of infection in the lung or gastrointestinal tract (9). The bacilli reach the liver via the hepatic artery or the portal vein (10). The prevalence of TLAs is 0.34% in patients with hepatic TB (20). TLAs commonly present with fever of unknown origin, anorexia, weight loss, and vague abdominal pain (10). Hepatomegaly is a common physical finding (21). Hypoproteinemia, elevated serum alkaline phosphates and mild hyperbilirubinemia are characteristic biochemical features (22).

The radiological findings of TLAs have a low specificity. Therefore, microbiological or pathological examination of specimens is needed to make a diagnosis and to distinguish from pyogenic and amoebic abscess or neoplasm of the liver (11, 22, 23). Rahmatulla et al. reported that the diagnosis of TLAs is usually made by laparotomy, due to the nondetection of percutaneous mycobacteria in the percutaneous liver aspirate (10). Recently PCR assay was demonstrated to be useful in the diagnosis of hepatic tuberculosis liver biopsy or aspirate, as in our case. The diagnosis can be confirmed by the patient's response to anti-TB drug therapy (11, 22).

Quadruple therapy with anti-TBC drugs for 1 year is recommended. Percutaneous drainage of the abscess, combined with systemic anti-TB chemotherapy, has been used in appropriate cases as an alternative to surgery (10, 22). Mustard et al. (24) treated TLAs by percutaneous drainage combined with trans-catheter infusion of anti-TBC drugs. Surgery is best reserved for multiple large lesions and lesions refractory to medical treatment (22).

In summary, ITB should be kept in mind as a cause of intestinal obstruction and perforation, especially in endemic areas. And TLAs should be thought of in the differential diagnosis of liver abscess, especially if there is primary TB in the gastrointestinal tract.

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Black Hairy Tongue Associated with Olanzapine Treatment:

A Case Report

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Abstract

Olanzapine is an atypical antipsychotic drug approved for acute and long-term treatment of bipolar disorder. Although relatively safe as compared to other classical antipsychotic medications, there are a number of uncommon adverse effects of olanzapine such as oral cavity lesions. In addition to the relatively common side effect of dry mouth, several articles have reported an association between olanzapine treatment and the development of oral lesions such as apthous stomatitis, pharyngitis, glossitis and oral ulceration. Although there are several cases in which the tongue was affected in conjunction with stomatitis or pharyngitis, we could not find a case report indicating a direct relationship between olanzapine use and a tongue lesion. We present here the case of a patient with bipolar disorder, who developed recurrent black hairy tongue on two different occasions following the addition of olanzapine to lithium treatment. In the present case, xerostomia (dry mouth), which is an adverse reaction of both olanzapine and lithium, may have played a role in the development of black hairy tongue. All agents with a possible side effect of xerostomia may predispose patients to black hairy tongue, especially when they are administered in combination. To preclude the development of this complication with such drugs, extra time and effort should be given to improving oral hygiene.

Key Words: Black hairy tongue, olanzapine, lithium, xerostomia, dry mouth, bipolar disorder, adverse effect.

Introduction

Olanzapine is an atypical antipsychotic drug approved for the acute and long-term treatment of bipolar disorder (1). It is considered an atypical antipsychotic because it alters affinities for serotonin and dopamine receptors. The most common adverse effects of olanzapine are somnolence, orthostatic hypotension, headache, constipation, weight gain, mild hyperglycemia, hypertriglyceridemia, extrapyramidal symptoms, dyspepsia and dry mouth (1, 2). Apart from these common side effects, there are a number of uncommon adverse effects of olanzapine, such as oral cavity lesions (3). Specifically, several authors have reported an association between olanzapine treatment and the development of such oral lesions as apthous stomatitis, pharyngitis, glossitis and oral ulceration (3, 4). Although several cases have been reported in which the tongue is affected in conjunction with stomatitis or pharyngitis (4), we could not find an article reporting a direct relationship between olanzapine use and a tongue lesion.

In this article, we present the case of a patient with a diagnosis of bipolar disorder, who developed recurrent black hairy tongue (BHT) on two different occasions following the addition of olanzapine to her treatment.

Case Report

A 25-year-old woman who presented with manic symptoms (i.e., euphoria, overtalkativeness, insomnia, grandiosity) to the emergency room, was admitted to our psychiatry inpatient clinic with a diagnosis of bipolar disorder I. Her psychiatric history revealed that the current admission was her fifth hospitalization since the beginning of her illness six years previously. Since her first episode, almost every year she had discontinued her treatment without consulting her physician. Each time, her nonadherence was eventually followed by the recurrence of manic symptoms and ended with hospitalization. During the first three hospitalizations, her symptoms were stabilized

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with a combined treatment of classical antipsychotic drugs (i.e., haloperidol, zuclopenthixol) and mood stabilizers (i.e., lithium, valproate). At the time of discharge in her first two hospitalizations, she was prescribed lithium (900 mg/day) as the mood stabilizer, and sodium valproate (1,000 mg/day) was added to the lithium therapy in the third one. In her last two hospitalizations (fourth and fifth), olanzapine (20 mg/day) was initiated as the antipsychotic drug concurrently with the mood stabilizers to decrease manic symptoms.

In the first month of her fourth hospitalization, while she was on the combined treatment of olanzapine (20 mg/day), lithium (900 mg/day), and sodium valproate (1,000 mg/day), she noticed discoloration at the back of her tongue. She also described alteration of taste and sensation of thickness in the dorsum of her tongue. She was not receiving any additional medications on a regular basis and was in good physical health except for the oral lesion. Her medical files did not reveal any history of diabetes mellitus or any other systemic illness. The blood levels of lithium and sodium valproate were within normal limits (0.7 mEq/L , 92.6μg/mL, respectively). There was no significant laboratory finding, including HIV and thyroid hormone levels. Her family and hospital staff confirmed that she regularly brushed her teeth and practiced daily oral hygiene. She had been smoking 1 – 2 cigarettes per day for the last 2 years, but she described her smoking as irregular. No use of alcohol or any illicit drug was described.

After physical examination, the diagnosis of BHT was made by a consultant dermatologist. A possible association between olanzapine and BHT was suspected, as the patient had already been using other medications for longer periods without any complication. Upon recommendations of the dermatologist, olanzapine treatment was discontinued. The patient was also advised to brush her tongue with a soft toothbrush two times a day, and give more care to her oral hygiene. Twenty days after the cessation of the drug, BHT completely disappeared. After her discharge from hospital, the patient was in full remission for 10 months, while she was using lithium and sodium valproate combination therapy. During this period there were no drug-related complications, including tongue lesions.

Ten months later, she had discontinued her drug treatment again, which resulted in her fifth (current) hospitalization (twelve months after her fourth hospitalization). The combined treatment of olanzapine (20 mg/day) and lithium (1,200 mg/day) was again reinstituted. As in her fourth hospitalization, she developed BHT after one month of therapy (Fig. 1). There were no significant changes in her medical status and smoking habit since her last hospitalization. The physical and neurological examinations were totally normal except for her tongue. The visual intraoral inspection revealed a localized bilateral dark brown hairy appearance at midline of the posterior dorsal tongue. The other parts of the tongue (tips and both sides) were not involved. The patient denied any pain or discomfort in the tongue. The consultant dermatologist confirmed the diagnosis and made recommendations similar to those made before. The consultant did not find it necessary to conduct further investigations, including culture or biopsy from the lesion. As the patient was displaying hypomanic symptoms while the BHT was recurring, we decided to continue olanzapine treatment at a lower dose (5 mg/day) instead of stopping it completely.

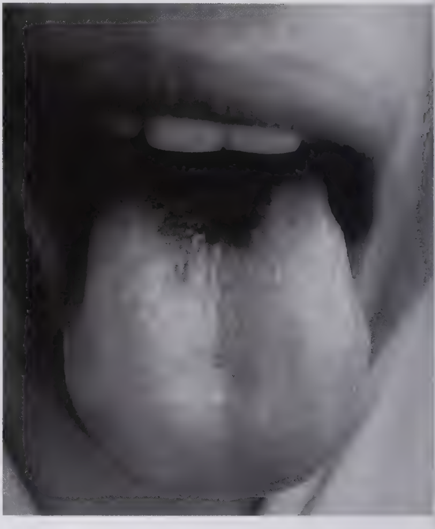

Fig. 1. Bilateral dark brown hairy appearance at midline of the posterior dorsal tongue.

Despite continuation of the lower dose of olanzapine, and the lithium treatment (1,200 mg/day), the BHT completely disappeared over the next three weeks (Fig. 2). The patient was discharged in good condition from the hospital, without any tongue lesions. At her follow-up visit in the fourth month after her discharge, she was free of any tongue lesions while using lithium alone.

Discussion

Black hairy tongue, also known as lingua villosa nigra, is an abnormal coating of the tongue re-

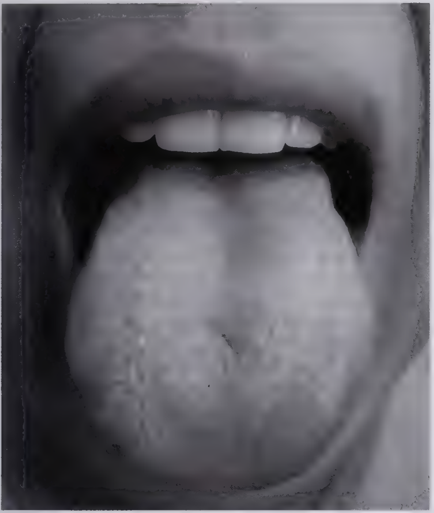

Fig. 2. The patient's tongue after lowering of olanzapine dose and empirical treatment.

sulting from elongation and lack of desquamation of the filiform lingual papillae (5–10). The hairy appearance is due to the elongation of keratinized filiform papillae, which may have different colors varying from white, yellow-brown to black depending upon the involved extrinsic factors (i.e., tobacco, coffee, tea or food) and intrinsic factors (i.e., chromogenic organisms in normal flora) (8, 10). Hairy tongue is diagnosed when filiform papillae are elongated more than 3 mm (7). This lesion is usually found on the dorsal tongue; it usually begins on the posterior tongue near the foramen cecum and then spreads laterally and anteriorly. The involvement of other parts of tongue is relatively rare (9).

The presentation of BHT is usually asymptomatic; however, in some cases like ours, symptoms such as alteration of taste, metallic taste, nausea or halitosis may be noted (5, 8). Occasionally, the papillae are so elongated that the patient may experience a tickling or gagging sensation in the soft palate during swallowing (5). In addition, overgrowth of candida albicans within elongated papillae may cause a variety of symptoms, such as glossopyrosis (burning tongue) (6).

The prevalence estimates of BHT vary widely, from 0.15–11.3% in the general population (7, 9). It has been observed with greater frequency in males, heavy smokers, intravenous drug users, edentulous patients, those who heavily drink coffee and tea, the elderly disabled and HIV patients (6, 10–13). Several precipitating factors have been implicated in the development of BHT, such as the use of broad-spectrum antibiotics (e.g., tetracycline, amoxicillin), the use of oxidizing mouthwashes or antacids, toothpastes containing neomycin, general debilitation due to old age, poor oral hygiene, heavy smoking, and radiation therapy (3, 6). Some other psychotropic drugs (i.e., phenothiazines, tricyclic antidepressants, benzodiazepines, thiothixene, tranylcypromine, fluoxetine) are also reported to be associated with BHT (3, 13).

Information about the pathogenesis of black hairy tongue is limited. *Candida* and *Aspergillus* can frequently be demonstrated in the cultures taken from the sides of the lesion. Cytological smears stained with Gram stain or periodic-acid-Schiff (PAS) stain may reveal candidal organisms in these tongue lesions (6). However they are not believed to be the causative agents (5). According to some authors, the limitation of tongue movements due to painful oral situation or other illnesses may be responsible for the development of hairy tongue (5, 14). The lack of tongue movements prevents the normal desquamation of the keratinized surface layers of the filiform papillae through friction of the tongue with food, the palate and the upper anterior teeth (14). This mechanism could be an explanation for the increased prevalence of BHT among the elderly and patients with chronic illness.

In our case, the patient developed BHT following the co-administration of olanzapine with lithium and valproate for stabilizing her acute manic symptoms. Although smoking (less than 2–3 cigarette per day) may have been partially responsible, BHT was not present until the co-administration of olanzapine with other drugs. Furthermore, the patient had already been taking other drugs (lithium throughout her course of treatment and sodium valproate for 10 months after her fourth hospitalization). The re-introduction of olanzapine treatment at a daily dose of 20 mg resulted in development of BHT at about the same time as in her previous admission. The rechallenge of olanzapine and resultant recurrence of BHT in one month corroborated the possible association between olanzapine and BHT. The BHT was treated successfully by lowering the dose of olanzapine and improving oral hygiene. In this patient, the relationship between olanzapine and BHT was possibly a dose-dependent relationship, as the sustained administration of olanzapine in lower doses (5 mg/day) did not cause progression or endurance of the lesion.

Apparently the xerostomia (dry mouth), which is an adverse reaction to olanzapine and to lithium, may have played a role in the pathogenesis of BHT (15). Dry mouth is a common adverse effect of treatment with lithium salts (3, 15). Although the most obvious feautre of this complaint is hyposalivation, other factors, such as the experience of thirst due to polyuria, may also play a role. On the other hand, olanzapine also causes dry mouth—at a relatively low incidence (16%)—by blocking both muscarinic cholinoceptors and alpha 1-adrenoceptors (1, 15). In the literature, it is consistently reported that drug combinations can increase the side effects of medications, particularly xerostomia (15). It is likely that concomitant administration of these two xerostomia-inducing agents (olanzapine and lithium) caused a cumulative effect which resulted in the development of BHT.

BHT is a benign and self-limiting condition (5, 6). Empirical approaches such as brushing or scraping the tongue, improving oral hygiene, and elimination of any potential offending factors (tobacco, candies, strong mouthwashes, antibiotics, etc.) would be sufficient to remove the lesions. Brushing or scraping the tongue would remove elongated filiform papillae and retard the growth of additional ones. Rinsing the mouth with diluted hydrogen peroxide may also help bleach the color. In most instances, the tongue returns to its normal state subsequent to physical debridement and proper oral hygiene (13). Other alternatives involve lifestyle management, which includes drinking lots of water and eating raw fruit and vegetables such as celery, apples and carrots to provide roughage on the tongue. If the etiology of a patient's BHT appears to be primarily due to poor oral hygiene, a consultation with a dentist is strongly suggested (5).

Pharmacological interventions are rarely required in the treatment of BHT. In the presence of superimposed candidal infection with consequent glossopyrosis, topical antifungal medications such as clotrimazole or nystatin could be used (6). In some other cases, topical retinoids, oral retinoids such as isotretinoin, topical triamcinolone acetonide, gentian violet, salicylic acid, vitamin B complex, and 40% urea solution, have been reported to be successful in the treatment of BHT. Yogurt or other *Lactobacillus acidophilus* cultures may be of benefit (5, 8, 16). Clipping of the elongated papillae (using local anesthesia) or surgical excision of the papillae is rarely required and is suggested only as a last resort. If the lesion persists, a consultation with a dentist would be appropriate, to rule out other clinically similar entities (6).

In conclusion, BHT may develop as an adverse reaction to olanzapine treatment, especially when combined with lithium. In the present case, the relationship between olanzapine and BHT was possibly a dose-dependent relationship, as the sustained administration of olanzapine in lower doses did not cause progression or permanency of the lesion. All agents with a possible side effect of xerostomia can be a source of BHT, especially when they are administered in combination. To preclude the development of this complication with such drugs, extra time and effort should be given to improving oral hygiene.

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Recurrent Episodes of Dermatomyositis-Associated Pneumonitis Masquerading as Hypersensitivity Pneumonitis

Bobbak Vahid, M.D., and Paul E. Marik, M.D.

Abstract

This case report describes a unique presentation of dermatomyositis-associated pneumonitis. A 44-year-old man presented with repeated episodes of fever, dyspnea, and hemoptysis accompanied with pulmonary infiltrates, on chest CT scan. Hypersensitivity pneumonitis was suspected. Further work-up showed clinical and serologic evidence of dermatomyositis-associated pneumonitis. The patient was treated with oral prednisone and azathioprine. The subject of dermatomyositis-associated pneumonitis is discussed.

Key Words: Hypersensitivity pneumonitis, dermatomyositis, interstitial lung disease.

Introduction

Dermatomyositis is a systemic inflammatory disease characterized by involvement of skeletal muscles and skin rash. Pulmonary involvement has been reported in 5 – 30% of patients with dermatomyositis (DM) and polymyositis (PM), and pulmonary disease has contributed to the death of 10% of patients in some case series. The dermatomyositis-associated pneumonitis may present as non-resolving pneumonia or acute respiratory failure (1, 2). Recurrent episodes of such pneumonitis mimicking hypersensitivity pneumonitis, as described in this case, are an unusual manifestation of this disease.

Case Report

A 44-year-old Caucasian male was referred to the pulmonary clinic for evaluation of his pulmonary disease. The patient had had three episodes of pneumonitis, hemoptysis, and respiratory failure in the preceding 6 months. The manifestations of pneumonitis included hemoptysis, fever, hypoxemia, and non-productive cough. Each episode was treated with antibiotics and corticosteroids. The patient also reported dyspnea with exertion, fatigue, diffuse muscle pain, diffuse arthralgia, and back pain. Close review of the course of his pulmonary disease suggested that the recurrence of pneumonitis corresponded to rapid taper of corticosteroids. The patient also had a history of gastroesophageal reflux disease, intermittent asthma, hypertension, and chronic sinusitis. His medications on presentation included amlodipine, esomeprazole, and montelukast. The patient was a lifelong non-smoker who worked as a jeweler and had been exposed to polishing wax (brand name: ZAM). He was evaluated in another center before presentation; while he was there, his lung disease was diagnosed as hypersensitivity pneumonitis secondary to polishing wax exposure.

Physical examination revealed bilateral pulmonary crackles, with normal cardiac, abdominal and neurological findings. Skin evaluation showed a symmetric, scaly, violaceous or erythematous eruption over the extensor surfaces of the metacarpophalangeal and interphalangeal joints of the fingers. Laboratory results included white blood cell count of 17.3×10^3/mL, normal creatinine, erythrocyte sedimentation rate of 10 mm/hr, normal serum complement levels, normal serum creatine phosphokinase (CK) levels, normal C-reactive protein, negative anti-nuclear antibody, negative

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P-ANCA, negative C-ANCA, and normal AST and ALT. Further evaluation showed high serum aldolase level and positive anti Jo-1-antibody. Fig. 1 shows chest computed tomography (CT) scan findings and Fig. 2 shows the lung biopsy that was obtained via bronchoscopy. The lung biopsy showed nonspecific interstitial pneumonitis. The Table shows the patient's pulmonary function testing results during the 6 months before presentation. The decrease in lung volumes and single breath CO diffusion capacity (DLCO) suggests progressive interstitial lung disease.

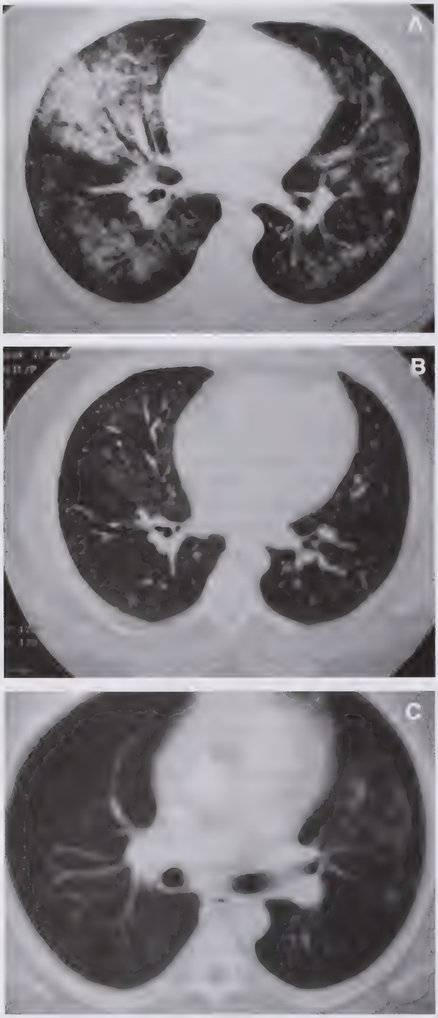

Fig. 1. **(A)** Chest CT scan showing bilateral patchy consolidations and ground-glass opacities 6 months before presentation. **(B)** Chest CT scan after a course of oral prednisone, showing complete resolution of infiltrates. **(C)** Chest CT scan 2 months before presentation, showing recurrence of pneumonitis.

Discussion

The findings of typical skin rash (Gottron's sign), muscle pain and weakness, high aldolase, positive anti Jo-1-antibody, and nonspecific interstitial pneumonitis (NSIP) are consistent with a diagnosis of dermatomyositis-associated interstitial lung disease. NSIP can also be seen in hypersensitivity pneumonitis, but hypersensitivity pneumonitis was excluded by simply observing further flare-ups of pneumonitis without exposure to workplace or polishing wax.

Pulmonary involvement has been reported in 5–30% of patients with DM and PM, and pulmonary disease has contributed to the death of some 10% of patients in some series (1, 3). Differential diagnosis of pulmonary involvement in DM-PM includes interstitial lung disease (ILD), infection, aspiration pneumonia, respiratory muscle weakness, and drug-induced lung disease. ILD with myositis is rarely associated with malignancy. A majority of patients with PM-DM-associated

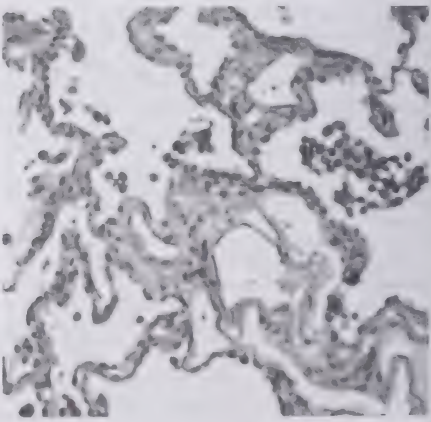

Fig. 2. Lung biopsy showing uniform involvement of lung parenchyma with prominent accumulation of alveolar macrophages, mild-to-moderate fibrosis of alveolar septae, and mild interstitial chronic inflammation consistent with nonspecific interstitial pneumonitis.

TABLE

Pulmonary Function Testing Showing Decrease in FVC and DLCO

	5 Months before Presentation	3 Months before Presentation	One Month before Presentation
FVC L(%predicted)	4.33 (92%)	3.61 (77%)	3.26 (70%)
FEV1L(%predicted)	3.88 (101%)	3.17 (82%)	2.81 (73%)
%FEV1	89%	88%	86%
TLC L(%predicted)	5.58 (90%)	4.65 (75%)	4.21 (68%)
DLCO ml/min/mmHg(%predicted)	28.72 (80%)	23.33 (65%)	19.7 (55%)

FEV1 = forced expiratory volume in the first 1 second of expiration; FVC = forced vital capacity; TLC = total lung capacity; DLCO = diffusing capacity for carbon monoxide.

ILD present with pulmonary symptoms mimicking community-acquired pneumonia that is refractory to antibiotic therapy. A less common presentation is fulminant course with adult respiratory syndrome (ARDS) and respiratory failure (1, 3).

Pulmonary involvement can precede, coincide with, or follow muscular and/or cutaneous manifestations of PM-DM (3). Antibodies directed against the aminoacyl tRNA synthetase, including anti Jo-1-antibody, are most specific for inflammatory myopathies and ILD. The antisynthetase antibodies are associated with fever, Raynaud's phenomenon, polyarthritis, myositis, and ILD (4). Histopathology of PM-DM-associated ILD includes NSIP, usual interstitial pneumonia (UIP), bronchiolitis obliterans with organizing pneumonia (BOOP), and diffuse alveolar damage (DAD) (2). Bronchoscopy and bronchoalveolar lavage may be helpful to exclude infection, but don't provide specific diagnostic information (4). Treatment always includes corticosteroids. Better prognosis has been observed in patients with organizing pneumonia, those with a predominantly active cellular infiltration rather than fibrosis on CT or lung biopsy, younger patients, and those with an elevated CK at the onset of ILD. Other reported treatments are azathioprine, methotrexate, pulse cyclophosphamide for initial remission, and hydroxychloroquine as a steroid-sparing agent (2, 5, 6).

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Metastatic Signet Ring Adenocarcinoma:

An Unusual Cause of Cardiac Constriction

ATHER ANIS, M.D., RAJEEV L. NARAYAN, M.D., SURAJ KAPA, M.D., MARC KLAPHOLZ, M.D.,
AND MUHAMED SARIC, M.D., PH.D.

Abstract

Pericardial constriction secondary to metastatic adenocarcinoma is exceedingly rare. We present the first recorded case of pericardial constriction secondary to metastatic signet-ring mucinous adenocarcinoma diagnosed by echocardiography. The cornerstones of echocardiographic diagnosis of constriction are the following: interventricular septal bounce phasic with respiration, M-mode recordings of the inferior vena cava, and the characteristic Doppler velocity patterns recorded from the mitral valve, hepatic veins, and mitral annulus.

Key words: Echocardiography, adenocarcinoma, cardiac constriction.

Case Report

A 59-YEAR-OLD AFRICAN-AMERICAN MAN with a long history of smoking tobacco and consuming excessive amounts of ethanol, came to the emergency department complaining of progressive chest pain, dyspnea, bilateral lower extremity edema, nausea and vomiting over the preceding month, along with more recent complaints of hoarseness and dysphagia.

Physical examination was significant for prominent jugular venous distension, S_4 gallop, dullness over the lung bases, ascites and 2+ pitting edema of both lower extremities. Laboratory data revealed iron deficiency anemia and an elevated serum carcinoembryonic antigen (CEA) level of 98.2 ng/mL (normal <3.0 ng/mL).

After the clinical diagnosis of congestive heart failure was established, chest radiograph and transthoracic echocardiogram (TTE) were obtained. Chest radiograph demonstrated bilateral pleural effusions and an elevated left hemidiaphragm. TTE revealed mild left ventricular (LV) hypertrophy and normal LV systolic function (LV ejection fraction of 60%). The size and function of the right heart were normal. Surrounding the epicardial surface of both ventricles and the right atrium was a 2–3-cm thick band of tissue extending into the pericardial transverse sinus along the ascending aorta (Fig. 1). The findings were sug-

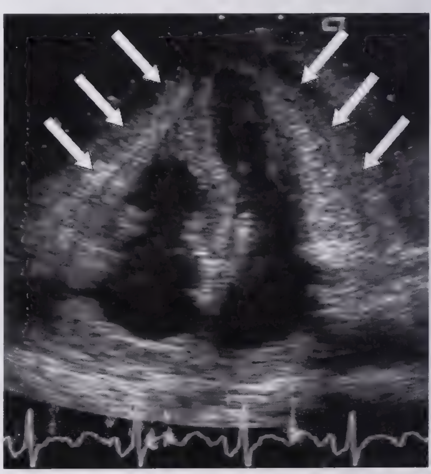

Fig. 1. Transthoracic echocardiogram in the apical 4-chamber view at end diastole reveals encasement of the heart by the signet-cell adenocarcinoma (arrows).

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gestive of either an organized pericardial effusion or a neoplastic invasion.

The presence of an interventricular septal bounce phasic with respiration was suggestive of constrictive physiology (1). The diagnosis of constriction was confirmed by Doppler velocity patterns of the mitral valve, hepatic veins and mitral annulus, as well as M-mode recordings of the inferior vena cava (IVC) (2).

Mitral Inflow

Spectral pulsed-wave Doppler recorded at the mitral valve leaflet tips, showed 66% respiratory variation in peak velocity of the mitral E wave with a short deceleration time (<150 msec) (Fig. 2).

Hepatic Vein

In the spectral pulsed-wave Doppler tracing of the hepatic vein, a marked expiratory enhancement in the peak velocity of the atrial reversal (AR) wave was noted (Fig. 3).

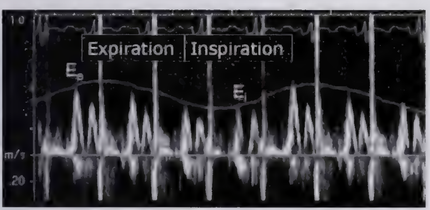

Fig. 2. Mitral blood inflow spectral pulsed-wave Doppler velocity tracings reveal a 66% respiratory variation (normal < 25%) in peak velocity of the mitral E wave (E_e = 70 cm/sec at end expiration; E_i = 42 cm/sec at end inspiration). Also note a very rapid deceleration of the E wave (<150 msec).

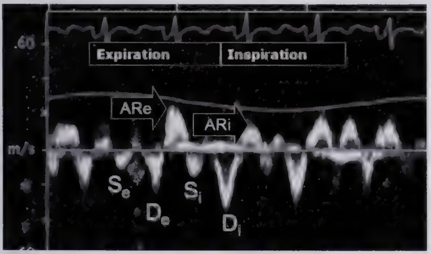

Fig. 3. Hepatic vein spectral pulsed-wave Doppler tracings demonstrate a marked expiratory enhancement in the peak velocity of the atrial reversal (AR) wave (AR_i = 14 cm/sec at end inspiration; AR_e = 26 cm/sec at end expiration). S and D refer to systolic and diastolic antergrade waves; the subscripts i and e refer to inspiration and expiration, respectively.

Mitral Annulus

Tissue Doppler recordings of the lateral mitral annulus showed a normal peak velocity of the early (E') wave at 17 cm/sec (normal >12 cm/sec) and an E'/E ratio of 0.44. Both findings were consistent with pericardial constriction but not myocardial restriction.

Inferior Vena Cava

During expiration, the IVC was dilated (diameter = 2.8 cm; normal < 2.5 cm). It collapsed less than 50% with inspiration (diameter = 1.9 cm) on M-mode recordings. This is indicative of a markedly elevated mean right atrial pressure (15 – 20 mm Hg), consistent with constrictive physiology. Pulmonary artery systolic pressure was estimated to be mildly elevated (35 – 40 mm Hg).

A double-contrast barium swallow esophagogram was normal. Five-millimeter axial computed tomography of the chest, abdomen and pelvis following oral and intravenous contrast administration revealed diffuse pericardial thickening, large bilateral pleural effusions and compressive lung atelectasis. In the abdomen, diffuse hepatomegaly with passive liver congestion and a large amount of ascites were noted. These findings were consistent with constrictive pericardial physiology. No abnormalities of the stomach, small bowel, colon or pancreas were found.

On surgical pericardiotomy a thickened pericardium with several irregularly shaped nodules in the pericardial fat were observed; no apparent abnormalities of the surrounding lung tissue were seen.

Surgical pathology revealed small-cell, signet-ring-type metastatic adenocarcinoma in the fibrous tissue of the pericardium with intralymphatic invasion of the surrounding adipose tissue. Mucicarmine staining confirmed the presence of a mucinous component and demonstrated CEA immunoreactivity.

The final diagnosis of a signet-ring-type adenocarcinoma of unknown primary location, leading to pericardial constriction, was established. While awaiting initiation of oncologic therapy, the patient had a cardiac arrest with pulseless electrical activity. Since his family refused autopsy, the immediate cause of death was not established.

Discussion

Pericardial constriction is characterized by an intractable encasement of the heart, which uncouples changes in intrapericardial pressures from those in the pleural space. This can ultimately lead to heart failure despite preserved systolic and diastolic function of the myocardium.

Historically, tuberculosis was the leading cause of constrictive pericarditis (3, 4). However, in the modern era a majority of cases are idiopathic (42 – 49%); other causes are post-cardiac surgery (11 – 37%), mediastinal radiation (9 – 31%), connective tissue disorder (3 – 7%), infections including tuberculosis (3 – 6%), and rarely malignancy, medications, trauma, sarcoidosis, uremic pericarditis or asbestosis (1 – 10%) (5 – 7).

The prevalence of pericardial constriction in patients with metastatic pericardial tumors is about 1 – 11% (8). As with other cardiac tumors, secondary tumors of the pericardium are more common than primary ones (9). Metastatic adenocarcinomas are a rare cause of pericardial constriction; most of them are bronchial in origin (10 – 12).

In our patient the primary origin of adenocarcinoma could not be established although the elevated CEA level pointed toward a primary adenocarcinoma of the gastrointestinal tract. Direct tumor invasion or lymphagitic spread was probably responsible for the constrictive physiology.

This appears to be the first case recorded in English of metastatic signet-ring type adenocarcinoma leading to pericardial constriction diagnosed by echocardiography. In the only other previously reported case, bronchial adenocarcinoma metastasized to the pericardium; the diagnosis of constriction was suggested by right heart catheterization, and echocardiogram was reported to be technically difficult (8).

In pericardial constriction, a rigid pericardium isolates the heart from normal transmission of intrathoracic pressure changes and leads to ventricular interdependence. Due to pericardial encasement, the normal decrease in intrathoracic pressure that occurs during inspiration is transmitted only to the pulmonary and systemic venous systems, but not to the cardiac chambers.

In constriction, normal negative-pressure inspiration leads to a pressure drop in the pulmonary veins but not in the left ventricle. This in turn results in a markedly decreased pressure gradient across the mitral valve, and thus diminished left ventricular filling. On the contrary, the drop in pressure in systemic veins enhances venous return and right ventricular filling.

Since cardiac volume of the constricted heart is fixed, during inspiration the right ventricle fills at the expense of the left ventricle, while the opposite occurs during expiration. As a consequence, during inspiration there is an abrupt posterior motion ("septal bounce") of the interventricular septum (IVS) during early diastole, due to rapid right heart filling, followed by flattening of IVS in mid-diastole and an abrupt anterior motion occurring after atrial contraction (1, 13).

Doppler flow velocity patterns through the mitral and tricuspid valves and hepatic vein not only provide insight into hemodynamic changes that occur during respiration in constrictive pericarditis, but also help differentiate it from restrictive cardiomyopathy.

On Doppler echocardiography, the typical pattern of constrictive pericarditis consists of:

1. An inspiratory drop of more than 25% in the peak velocity of the early left ventricle diastolic filling wave (mitral E wave);
2. Deceleration time of mitral E wave less than 160 milliseconds;
3. An increase in the left ventricle isovolumic relaxation time with inspiration;
4. An increase in diastolic flow reversal with expiration in the hepatic veins (2, 14).
5. Doppler echocardiography with respiratory recordings has a sensitivity of 88% for the diagnosis of constrictive pericarditis (2).

On mitral annular pulsed-wave tissue Doppler imaging, the peak velocity of the early diastolic wave (e' wave) is not diminished in constrictive pericarditis. This finding distinguishes constrictive pericarditis from restrictive cardiomyopathy, in which the diastolic mitral annulus velocities are diminished (15, 16). In addition, the restrictive pattern is characterized by a predominantly inspiratory increase in diastolic flow reversal in hepatic veins (2).

Our case underscores the importance of echocardiography in the diagnosis of cardiac constriction, as the clinical presentation may be very nonspecific.

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Abstracts

The following abstracts were presented by investigators at the Twenty-Second Annual Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine Research Day on May 31, 2006. Most of the investigators serve in the Samuel Bronfman Department of Medicine, including those working at affiliated institutions such as the Bronx Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Elmhurst, NY; Queens Hospital Center, Jamaica, NY; and St. Joseph's Hospital and Medical Center, Paterson, NJ. Abstracts from Queens Hospital Center and Jersey City Medical Center were presented as posters on Research Day, held on May 10, 2006 and May 24, 2006, respectively.

Mount Sinai School of Medicine

Low Viral Load Chronic Hepatitis B and Liver Histology. R. Akhtar and D. Dieterich. Department of Internal Medicine, Division of Liver Disease. Mount Sinai School of Medicine, New York, NY.

Background: Chronic hepatitis B is associated with high morbidity and mortality. Liver biopsy is recommended to assess the degree of liver damage in these patients. In hepatitis B e antigen (HBeAg)-negative patients, current guidelines advise the consideration of treatment once an elevation of alanine aminotransferase (ALT) levels greater than two times the upper limit of normal is observed, or moderate to severe hepatitis is discovered on biopsy. In our cohort, we describe the liver histology in patients with HBeAg-negative chronic hepatitis B associated with viral loads of HBV DNA less than 10^5 international units (IU) per milliliter.

Methods: A total of five HBeAg-negative patients (labeled A through E), naïve to treatment, underwent liver biopsy. The patients' charts were reviewed to assess demographics, comorbidities, alcohol use, previous hepatitis workup, and medications. The liver biopsy specimens were reviewed by the Department of Pathology and scored using a modified Histology Activity Index grading scale to describe the presence of necrosis and inflammation, and a modified staging scale to describe architectural changes, fibrosis, and cirrhosis.

Results: Patient A had mild to moderate interface hepatitis, no confluent necrosis, moderate portal inflammation, and fibrous expansion of most portal areas. At the time of biopsy, the patient's ALT was 35 units/L with a viral load of 51,400 IU/mL. Patient B had mild to moderate interface hepatitis, no confluent necrosis, mild portal inflammation, and fibrous expansion of most portal areas with occasional portal-to-portal bridging. This patient's ALT was 128 units per liter associated with a viral load of 100 IU/mL. Patient C had mild interface hepatitis, no confluent necrosis, mild portal inflammation, and fibrous expansion of only some portal areas. Patient C's ALT was 26 units per liter with a viral load of 100 IU/mL. Patient D had mild-to-moderate periseptal interface hepatitis, no confluent necrosis, moderate portal inflammation, and fibrous expansion of most portal areas with some short fibrous septa. This patient's ALT was 25 units/L with a viral load of 340 IU/mL. Finally, patient E had mild-to-moderate periportal interface hepatitis, no confluent necrosis, mild portal inflammation, and fibrous expansion of some portal areas. These findings were associated with an ALT of 18 units/L and a viral load of 19,100 IU/mL.

The viral loads of all five patients never measured above 10^5 international units (IU) per milliliter. Three of five patients (A, C, and E) had a history of alcohol use but denied current, regular drinking. In addition, all patients had normal levels of bilirubin, albumin, and prothrombin time while also testing negative for hepatitis C co-infection. Patients B and E had a history of hypertriglyceridemia now under treatment.

Conclusion: In patients with HBeAg-negative chronic hepatitis B, advanced findings on liver biopsy may exist with viral loads less than 10^5 copies/mL. Previous studies have identified patients with fibrosis despite normal liver function tests. However, liver damage with lower viral titers is not as well described. A larger cohort is needed to determine if these patients represent a substantial minority of the chronic hepatitis B patient population. It is conceivable that current treatment standards need to be modified to include patients with lower viral loads to prevent disease progression.

Prediction of Cases of Pneumocystis carinii Pneumonia (PCP) Pneumonia in Russia in the Absence of Prophylaxis. Lessons for Future Preparation. E. Alexander and J.R. Masci. Mount Sinai Medical Center, Elmhurst Hospital Center, Queens, NY.

Background: Data on patients with HIV/AIDS in Orenberg, Russia suggests a low rate of treatment with antiretroviral therapy/preventive therapy for PCP. Given this trend, we estimate the number of expected cases of PCP in Orenberg over the next two years.

Methods: Using data on a cohort of 59 patients from the American International Health Alliance partnership between Orenberg, Russia and Elmhurst, NY and prior data on incidence and prevalence of Pneumocystis in patients with HIV/AIDS in Europe, we calculated an expected prevalence of *Pneumocystis pneumonia* in Orenberg over the next 2 years.

Results: PCP is one of the most common AIDS-defining illnesses in the US and Europe. In the US, the frequency of PCP in AIDS patients is between 35 and 40%. In Europe, the prevalence of PCP in AIDS patients is 39%, with an incidence of 20.7/100 person-years. This would suggest an overall prevalence of PCP of approximately 40% in patients with AIDS, and an incidence of up to 20/100 person-years. Several studies however have shown regional and seasonal variations in both the incidence and prevalence of PCP, with decreased incidence in eastern and southwestern Europe and a prevalence of PCP in patients with AIDS as low as 5.5%.

As of 2003, a total of 11,587 cases of HIV were reported a city of 500,000 in central Russia. Assuming 15% of these patients have AIDS, the at-risk population for PCP is 1,738. We estimate that, based on the number of patients in this city with AIDS, and the above ranges for incidence and prevalence of PCP, between 88 and 707 patients could currently have PCP with up to an additional 353 patients developing PCP within the next year.

Conclusion: Despite studies of HIV in Eastern Europe which suggest a low incidence and prevalence of PCP compared with the US/Western Europe, Russia remains at risk for a large patient load with PCP. Bactrim PCP prophylaxis is an effective and low cost means to reducing the incidence of PCP in at-risk patients. It should be routinely prescribed for all HIV+ patients with CD4 <200 cells/mm^3.

Do the Cockcroft-Gault and MDRD Equations Give Similar Estimates of Kidney Function in an Amulatory Elderly Population? M. Bogaisky[1], S. Josyula[2], J. Winston[2], M. Swidler[1,2], and C. Wyatt[2]. [1]Geriatrics and [2]Medicine, Mount Sinai Medical School, New York, NY.

Background: Expert guidelines recommend use of either the Cockroft-Gault (CG) or the MDRD equation for the estimation of kidney function in adults. However, neither equation has been well-validated in elderly adults. It has also not been shown that the two provide similar estimates of kidney function in an ambulatory elderly population.

Objective: To determine if the CG and the MDRD equations yield clinically significant differences in estimates of kidney function in an ambulatory elderly population.

Methods: Data from all patients over the age of 65 seen in a geriatric clinic from August 1, 2004 to August 1, 2005 were abstracted. The most recent outpatient creatinine was chosen. To exclude patients with acute renal failure, those with a creatinine greater than 0.2 mg/dL above their recent baseline values or with only one recorded creatinine were excluded. The standard version of the CG equation and the simplified version of the MDRD equation were used. For the CG equation, the closest weight within one month of the creatinine assay was used and results were not adjusted for body surface area.

Results: A total of 1,264 of 1,990 subjects met criteria to compute both an MDRD and CG estimate of GFR. The average age was 81.4 (SD:

7.6), 80% were female, 40% white, 27% black and 31% Hispanic. When stratified by stage of chronic kidney disease (GFR<15,15–29, 30–59,60–89 and ≥90) 61% of subjects were staged differently by the two equations. In 92% of these cases the CG placed subjects in a worse stage than the MDRD. The average difference in GFR between the CG and MDRD estimates in these cases was 26.2 mL/min (SD: 19.5). In 116 subjects (9.2% of the population) the CG GFR was <30 while the MDRD was >30 (mean difference=22.8 mL/min, SD: 11.6). The CG equation found 60% of subjects with a GFR <60 while the MDRD gave only 25% of subjects a GFR <60.

Conclusions: The Cockroft-Gault and MDRD equations yield clinically significant differences in estimates of kidney function when applied to an elderly ambulatory clinic population. The Cockroft-Gault equation was more conservative. Validation of these equations in the elderly against a gold standard measurement is necessary.

Nuclear Import of Dendrin, a Novel Glomerular Slit Diaphragm Protein. K. Campbell and P. Mundel. Department of Medicine, Division of Nephrology, Mount Sinai School of Medicine, New York, NY.

Kidney podocytes and their slit diaphragms form the final barrier to urinary protein loss. There is mounting evidence that slit diaphragm proteins may participate in signaling pathways.

Dendrin, a protein originally identified in telencephalic dendrites, is a novel constituent of the slit diaphragm signaling complex where it binds to nephrin and CD2AP. In experimental crescentic glomerulonephritis, dendrin relocates from the slit diaphragm to the nucleus of injured podocytes. Functionally, in heterologous cells, dendrin increases AP1 signaling. The AP1 signaling requires the nuclear import of dendrin because it is significantly impaired in cells transfected with a dendrin construct lacking a functional nuclear localization signal.

Nuclear accumulation of dendrin is abrogated in podocytes cultured in serum-starved medium containing 0.2% fetal bovine serum. Futhermore, exposure of serum-starved cultured podocytes transforming growth factor-beta (TGF- β) at a dose sufficient to induce apoptosis (5 ng/mL) stimulated nuclear accumulation of dendrin noted as early as 30 minutes.

Nuclear expression of dendrin is associated with enhanced TGF-β and staurosporine-induced apoptosis in HEK 293 cells as determined by an Annexin-V based apoptosis assay.

These results suggest a novel signaling pathway whereby dendrin is shuttled from the glomerular slit diaphragm to the podocyte nucleus in the setting of TGF-β mediated apoptosis where it exerts pro-apoptotic effects by increasing the expression of as yet unidentified genetic targets.

Validation Study of a Semi-automated Program for Quantification of Atherosclerotic Burden by Magnetic Resonance Imaging. B.G. Choi[1], C.A. Novoselsky[2], G. Vilahur[1], D. Yadegar[3], and J.J. Badimon[1]; [1]The Mount Sinai Hospital, New York, NY; [2]Cabrini Medical Center, New York, NY; and [2]Lenox Hill Hospital, New York, NY.

Introduction: Practical implementation of magnetic resonance imaging (MRI) for the noninvasive screening of atherosclerosis is limited by inter- and intra-observer variability and labor intensity of morphometric analysis by manual planimetry (MANU).

Hypothesis: We assessed the hypothesis that a semi-automated quantification program (AUTO) for MRI would be faster and more accurate than MANU without loss of reliability.

Methods: Transverse images of the carotid arteries of asymptomatic hyperlipidemic patients (n=17) were obtained by 1.5T whole-body MRI with a 4-element phased-array coil. AUTO, programmed on ImageJ (NIH; Bethesda, MD), segments the images by change in signal intensity from lumen center to vessel outer wall in a serial circular array: lumen area (LA) is lumen center to lumen wall; vessel wall area (VWA) is lumen wall to vessel outer wall; vessel wall thickness is linear distance from lumen wall to vessel outer wall. Automated image post-processing with observer supervision identifies and corrects outlier segments. Images were each processed twice by two independent observers who repeated the same analysis by MANU. *In vivo* imaging of rabbits with atherosclerotic aortas (n=3) was similarly obtained and then sacrificed to confirm histopathologic correlation.

Results: Analysis time per image (seconds±SD) was 17.4±3.1 (AUTO) versus 87.3±19.4 (MANU), p<0.001. Inter- and intra-observer differences for carotid measurements were not significant for both AUTO and MANU (see Table); however, there was stronger correlation between animal histopathology and AUTO (r=0.87, p<0.0001) than with MANU (r=0.74, p<0.0001). Bland-Altman analysis did not demonstrate any systematic bias.

Conclusion: AUTO is superior to MANU in speed and histopathologic correlation without significant differences in inter- and intra-observer variability. Implementation of AUTO may facilitate MRI for the screening of the burden of atherosclerotic disease.

TABLE

Mean Inter- and Intra-observer Differences between Observations

		Lumen Area (%)	Vessel Wall Area (%)	Vessel Wall Thickness (%)
M	Interobserver	6.6	4.6	5.3
A		(p=0.32)	(p=0.27)	(p=0.09)
N	Intraobserver	2.8	3.0	2.3
U		(p=0.68)	(p=0.47)	(p=0.47)
A	Interobserver	3.9	4.0	4.2
U		(p=0.50)	(p=0.45)	(p=0.61)
T	Intraobserver	0.7	2.1	0.2
O		(p=0.91)	(p=0.70)	(p=0.96)

Platelet Function in Clopidogrel-Treated Subjects is Recoverable by Addition of Donated Platelets: Implications for Urgent Surgical Management in Acute Coronary Syndrome. B.G. Choi[1,2], G. Vilahur[1], M.U. Zafar[1,2], J.F. Viles-Gonzalez[1], V. Fuster[2], and J.J. Badimon[1,2]. [1]Cardiovascular Biology Research Laboratory and [2]Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Background: Aspirin (ASA) and clopidogrel are commonly used in the treatment of acute coronary syndrome, but their long anti-platelet effect may delay surgery if required. We studied the possibility of normalizing platelet reactivity after clopidogrel + ASA treatment.

Methods: We performed a randomized cross-over study of healthy subjects (n=11, age 35 ± 5 years) receiving a loading dose of either 300-mg or 600-mg clopidogrel + 325 mg ASA, followed by 75 mg clopidogrel + 81 mg ASA daily for 2 days. Platelet reactivity was assessed by light transmittance aggregometry (LTA) and flow cytometry pre-treatment, 4h- and 72h- post-load. To normalize platelet reactivity, increasing amounts of pooled platelets (20%, 40%, 50%, and 60% of total platelet rich plasma [PRP] volume) from 5 untreated volunteers (pooled V-PRP) were added *ex vivo* to the subjects treated PRP (S-PRP). Adenosine diphosphate (ADP) (10 μ M), arachidonic acid (AA) (1 mM), collagen (2 and 5 μg/mL), and TRAP (10μ M) served as agonists. By flow cytometry, we assessed activation by GPIIb/IIIa receptor exposure in the ADP-stimulated platelets.

Results: At both 4- and 72-h post-treatment, addition of 50% (300 mg arm) and 60% (600 mg arm) of V-PRP normalized ADP-induced platelet aggregation. Recovery of function was linear with each incremental increase of V-PRP. Addition of 20% V-PRP normalized platelet reactivity when challenged by TRAP whereas 40% V-PRP was required to normalize platelet function to AA and collagen at both 4- and 72-h. A minimum of 40% or 50% V-PRP were needed to overcome platelet disaggregation in the 300 mg or 600 mg arms, respectively. ADP-induced GPIIb/IIIa activation showed the same pattern as LTA (r=0.74).

Conclusions: Pre-operative transfusion of 10 platelet units (the equivalent of 40% V-PRP, see Table) after 300 mg clopidogrel loading or 15 units after 600 mg loading may reverse clopidogrel-induced platelet disaggregation. These doses *ex vivo* also fully normalized the response to AA and collagen. Pre-operative prophylactic transfusion may allow patients to benefit from clopidogrel's anti-platelet effect to the time of transfusion, shorten hospitalization, and decrease post-operative bleeding. Our findings deserve to be fully explored in a clinical trial.

TABLE

Dose Conversion Table for V-PRP to Platelet Units

% Added Pooled V-PRP	Platelet Units	Platelet Pools
20%	7.5	1–2
40%	10	2
50%	15	3
60%	22.5	4–5

Assumptions: One platelet pool increases platelet count by $10{,}000/\mu$L, 5 platelet units = 1 platelet pool, mean platelet count 150×10^6.

Selective Estrogen Receptor Modulation Reduces Characteristics of Plaque Vulnerability. B.G. Choi[1,2], G. Vilahur[1], M.U. Zafar[1,2], L. Cardoso[3], D. Yadegar[1], J.F. Viles-Gonzalez[1], M.B. Schaffler[3], V. Fuster[2], and J.J. Badimon[1,2] . Cardiovascular Biology Research Laboratory[1], Zena and Michael A. Wiener Cardiovascular Institute[2], Leni and Peter W. May Department of Orthopaedics[3], Mount Sinai School of Medicine, New York, NY.

Objectives: We assessed the hypothesis that selective estrogen receptor modulation with raloxifene induces changes in atherosclerotic lesions to a more stable plaque phenotype.

Background: Estrogen therapy (ET) is associated with increased cardiovascular events in post-menopausal women, but post-hoc analysis from an osteoporosis treatment trial (the Multiple Outcomes of Raloxifene Evaluation, MORE) conducted in the 1990s suggests that raloxifene decreased cardiovascular events in high-risk women, i.e., those most likely to have preexisting atherosclerotic lesions. The modern Raloxifene Use for the Heart (RUTH) study seeks to confirm whether this benefit is sustained on top of optimal pharmacologic therapy for coronary artery disease, but a mechanism of action for raloxifene's putative cardiovascular benefit is unclear. Some studies suggest an anti-inflammatory effect unlike ET; furthermore, *in vitro* studies point to possible changes in the morphology of vascular calcification with raloxifene that may have implications upon plaque stability.

Methods: Atherosclerosis was induced in 42 ovariectomized New Zealand White rabbits. The animals were then imaged by magnetic resonance (MRI) for baseline atherosclerosis measurement and randomized to control (OVX, n=12), raloxifene therapy (RLX, n=24), or immediate sacrifice (n=6) for immunohistopathologic correlation of MRI observations. Six months after randomization, rabbits underwent repeat MRI and then sacrifice for *ex vivo* micro-computed tomography (μCT) and molecular analysis.

Results: Unlike OVX, RLX significantly reduced the atheroma volume of previously established lesions ($-5.5 \pm 4.5\%$, $p<0.05$) as assessed by MRI; histopathologic analysis indicated volume reduction from 35% less lipid deposition ($p<0.05$) and 37% less macrophage content ($p<0.05$). Analysis for lesion inflammation revealed significant reductions (all $p<0.05$) in cyclooxygenase-2 (COX-2) by 60%, matrix metalloproteinase-1 by 50%, and monocyte chemoattractant protein-1 expression by 27% in RLX vs. OVX. μCT showed similar total vascular calcification between groups, but calcifications in RLX were less nodular and had better radial organization (mean calcific arc angle $63 \pm 7°$ vs. $33 \pm 6°$ in OVX, $p<0.01$), the predicted result of a 53% increase in bone morphogenetic protein-2 expression ($p<0.05$). The changes in plaque activity appear to be mediated through raloxifene's effect on estrogen receptor α which doubled in expression in RLX ($p<0.001$). Notably despite COX-2 inhibition, arterial whole-blood platelet aggregation in decreased when challenged by adenosine diphosphate ($p<0.01$).

Conclusions: Treatment with raloxifene results in regression of established atherosclerotic lesions, enhanced formation of calcification in a pattern associated with plaque stability, and decreased inflammation. Collectively these observations suggest that raloxifene may not have a deleterious effect on plaque stability.

Adjusting CPK Measurements for LV Mass to Determine Infarct Severity. S. Choudry, G. Lanier, L.B. Croft, and M.E. Goldman. Mount Sinai School of Medicine, New York, NY.

Background: Serum creatinine phosphokinase (CPK) levels have been shown to correlate with the mass of cardiac tissue that is damaged during a myocardial infarction (MI), and infarct size in turn has been correlated with prognosis. However, quantification of infarct size based solely on serum CPK levels, while supplying information about the mass of infarcted tissue, does not account for a patient's total ventricular mass. This method, therefore, may misrepresent the severity of an infarct in those patients with smaller or larger left ventricular (LV) mass. Adjustment of CPK levels for LV mass may provide a more accurate assessment of infarct severity, and therefore prognosis, in a given patient.

Methods: A retrospective cohort analysis was performed. Patients were selected for inclusion in the study from a review of all consecutive admissions to the Coronary Care Unit at Mount Sinai Hospital from July 2004 until December 2005. Patients with renal insufficiency, symptoms of chest pain lasting more than 24 hours, documented previous MI, or known prior LV dysfunction were excluded from the study. Patient demographic information, cardiac catheterization data, and echocardiographic parameters (when available), were recorded. The collected data was then analyzed for significant relationships between enzymatic measures of infarct size, LV mass, and degree of LV dysfunction.

Results: Sixty-two patients met the inclusion criteria for our study. No significant relationship between enzymatic measures of infarct size and degree of LV dysfunction was found. However, we found a significant relationship between left ventricular mass, as measured by echo, and body surface area (BSA) ($r=0.6046$, $p=0.007$). It is also notable that patients with a larger BSA had a significantly larger CPK than those with a smaller BSA (mean CPK 1001 vs. 605, $p=0.047$). In the subgroup of patients with a large MI, the patient's BSA significantly correlated with CPK at the time of catheterization ($r=0.4172$, $p=0.04$).

Conclusion: No significant relationship could be seen between enzymatic measures of infarct size and LV dysfunction when adjusted for left ventricular mass. This may be due to the small size of our study. Interestingly, patients with a larger BSA were found to have significantly higher enzymatic markers of MI. This suggests that an MI may be more difficult to detect in those patients with a smaller BSA, a finding that would need to be confirmed in larger studies.

Realistic Expectations about Publication Following a Year of Clinical Research. B. Cohen, E. Friedman, and K. Zier. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Purpose of Study: Many medical students who undertake a one year research fellowship expect that their work will result in a publication. Moreover, residency directors may hold the same expectation. The objective of this study was to document the publication rates of participants in one year research programs to provide a reasonable standard against which to judge productivity.

Methodology: Names of students and their mentors who participated in the NIH Clinical Research Training Program (CRTP) and the Doris Duke Clinical Research Fellowship from 2001 – 2004 were provided by the programs. Publications resulting from the fellowship year were tracked up to 18 months post-fellowship using PubMed.

Summary of Results: From 7/2001 to 6/2004, of 217 fellows, 24% had at least 1 publication 6 months post-fellowship. Publication rates increased with time, with 50% publishing 18 months after program completion. 69% of fellows who published had at least one first author publication. 55% of the publications generated by 6 months were original research, 34% were review articles, and 11% were case reports.

Conclusions: The results demonstrate that although about half of the participants in these programs are able to publish within 18 months of completion of their fellowship, since most participants complete their fellowships after their third year of school, only a minority will have published by the time they apply for residency. This information should provide Deans (Student Affairs, Research), students, and program directors with more realistic expectations for the outcomes of this medical school research experience.

SPECT Myocardial Perfusion Imaging in Morbidly Obese Patients: Image Quality, Hemodynamic Response to Pharmacologic Stress, and Diagnostic and Prognostic Value. W.L. Duvall, L.B. Croft, J.S. Corriel, A.J. Einstein, J.E. Fisher, P.S. Haynes, R.K. Rose, and M.J. Henzlova. Mount Sinai School of Medicine, New York, NY.

Background: Obesity is a growing epidemic in the United States, and little is known about the characteristics of the morbidly obese population (body mass index [BMI] >40 kg/m^2) undergoing stress myocardial perfusion imaging (MPI).

Methods and Results: We retrospectively reviewed all consecutive morbidly obese patients without known coronary artery disease presenting for a clinically indicated technetium 99m gated stress single photon emission computed tomography imaging study over a 42-month period. Studies were analyzed for image quality, for the contribution of attenuation correction to image interpretation, and for the hemodynamic response to pharmacologic stress. In patients who subsequently had cardiac catheterization, the results were compared with those from the initial MPI study, and the Social Security Death Index and hospital medical records were searched to the assess survival rate in the entire cohort. A total of 433 patients were identified with a mean BMI of 47.3 ± 8 kg/m^2 and a mean Tc-99m stress dose of 35.6 ± 5.4 mCi. Image quality was good in 61% of the patients, adequate in 37%, and poor in 2%. It was found to be dependent on the stressor used (better with exercise) but did not correlate with increasing weight or BMI. Attenuation correction was used in 95% of the studies reviewed and was helpful for image interpretation in 60%. The heart rate response to dipyridamole and adenosine was more pronounced and the blood pressure response to dipyridamole was less pronounced in morbidly obese patients compared with nonobese control patients. In the 43 patients who underwent catheterization, stress MPI had a sensitivity of 95% and negative predictive value of 80%. Kaplan-Meier survival analysis at 1 year showed a significant difference in survival rate of 98.3% for normal MPI studies and 94.0% for abnormal MPI studies ($p = 0.02$).

Conclusion: Diagnostic-quality single photon emission computed tomography imaging is feasible in the majority (98%) of morbidly obese patients with the use of a dual-head camera, attenuation correction, and high stress Tc-99m tracer doses. Exercise stress was associated with better image quality. The prognostic value of a normal MPI study in this population appears to be less favorable than in non-morbidly obese patients (J Nucl Cardiol 2006; 13:202–209).

AL Amyloid and Rheumatic Disease: Cause and Consequence. J.T. Diep, H. Blumstein, A. Solomon, D. Weiss, C.L. Murphy, Q. Guo, and P.D. Gorevic. Departments of Medicine, University of Tennessee at Knoxville, and Mount Sinai School of Medicine. New York, NY.

Background: Although secondary (AA) amyloidosis is well recognized as an uncommon complication of rheumatoid arthritis or spondyloarthropathy, relationships between amyloid due to immunoglobulin light chain deposition (AL) and rheumatic disease have been less appreciated. AL may be organ-dominant, or may involve multiple organ systems; it may simulate Sjogren's syndrome (SS), rheumatoid arthritis, polymyalgia rheumatica/giant cell arteritis, and rarely scleroderma.

Methods: AL subunit proteins were characterized from either formalin-fixed or frozen tissue by microsequencing. V-region gene amplification and sequence analysis was used for the identification of specific precursor light chain production in bone marrow, and to correlate with germ-line, rearranged Vλ3r genes in the normal PBMC repertoire, and those mutated / significantly overrepresented in AL amyloid.

Results: We reviewed five patients with AL amyloidosis and rheumatic disease; four with a Sjogren's-like syndrome and one presenting as a scleroderma-like illness. Type of amyloid was established by immunohistology, or by microsequencing. Localized AL in SS presented as cutaneous nodules (1), a waxy macular lesion (1), or multiple pulmonary nodules (amyloidomas), with no evidence of systemic deposits; in one patient however, pinch purpura biopsied as AL, leading to the recognition of gammopathy, visceral amyloid, and plasma cell dyscrasia. The fifth patient presented with a scleroderma-like illness, consisting of tightening skin, decreased oral aperture, dysphagia and myalgias. Recognition of atypical features led to a deep skin and muscle biopsy that showed amyloidosis; further work-up revealed monoclonal λ light chains in serum and urine, lytic lesions typical of multiple myeloma, and 40% plasma cells in bone marrow. Microsequence analysis of Bence-Jones protein (BJP) and amyloid peptides extracted from the formalin-fixed skin biopsy yielded residues 3-21 (FR1) and 40-53 (FR2) of a λ3r light chain, the germ-line sequence of which was used to amplify and sequence the entire V-region gene by amplification from a single slide of unfixed bone marrow.

Conclusion: The association between AL and Sjogren's- or scleroderma-like diseases is reviewed, and may be the result of systemic disease leading to the diagnosis of myeloma, or organ-specific amyloid in which localization may reflect structural features of specific light chains and/or an antigen-driven pathogenic mechanism.

The Regulation of the Maxi-K Channel in the Distal Nephron. G. Estilo. Mount Sinai School of Medicine, New York, NY.

Within the kidney, the connecting tubule (CNT) and the cortical collecting duct (CCD) are primarily responsible for K secretion. Two apical K-selective channels have been functionally identified in the CNT and CCD: the secretory K (SK) and the maxi-K (BK) channel. Whereas the SK channel mediates baseline K secretion, the maxi-K channel is considered to be involved in flow-stimulated K secretion. The renal response to dietary K loading includes an increase in urinary K excretion, due in large part to enhanced K secretion in the distal nephron. Recent data from our group has demonstrated a role for the maxi-K channel in renal K adaptation. Dietary K loading led to an increase in abundance of maxi-K mRNA transcripts, enhanced flow-stimulated net K secretion in microperfused CCDs, and a redistribution of immunodetectable channel proteins from an intracellular pool to the apical membrane. This adaptation could be mediated by a transient increase in plasma K concentration but could also be initiated by a dietary K-induced increase in circulating levels of aldosterone. To test our hypothesis that aldosterone regulates maxi-K channel expression and activity in the CCD, New Zealand white rabbits were fed low Na and high Na diets, the former to increase circulating levels of aldosterone, for 10 days. At time of sacrifice, serum and urine were collected for measurement of Na, K, and aldosterone concentrations, results of which are depicted in the **Table** below. As expected, rabbits fed the low Na diet excreted no urinary Na and had higher circulating levels of aldosterone than the rabbits fed the high Na diet. There were no significant differences between serum [Na] and [K] in the two experimental groups. Real-time PCR quantitation of mRNA encoding maxi-K α- and β- subunits in isolated CCDs from high Na and low Na-fed rabbits are being analyzed. Indirect immunofluorescence microscopy will also be utilized to study the effects of aldosterone on localization of channel proteins. Preliminary data from a single transport study of a CCD isolated from a low Na-fed rabbit demonstrated an increase in net K secretion and Na absorption as tubular flow rate was increased from slow physiologic (~1 nL·min^{-1}·mm^{-1}) to fast (~5 nL·min^{1}·mm^{1}). This data suggests that aldosterone, in the setting of normokalemia, stimulates maxi-K channel expression activity in the distal nephron.

How Much Time Do Geriatricians Spend in Nonreimbursable Care Coordination? J. Farber. Mount Sinai School of Medicine, New York, NY.

Background: Geriatrics practice involves nonreimbursed care coordination interactions with patients, caregivers and others outside the office visit. The purpose of this study is to describe the amount and nature of time geriatricians spend providing nonreimbursable care coordination.

Methods: Physicians in a large academic geriatric ambulatory practice with at least two half-days of office visits scheduled in the week were selected to participate. Participants were briefed and provided a written protocol, along with structured interaction forms to document all clinical interactions outside of office visits during one of three randomly selected one-week periods from November 2005 through January 2006. Physicians were encouraged to complete the interaction forms at the time the work was performed to minimize uncaptured events and to document time spent to the nearest minute. Information about the participant in the interaction, and the mode, nature and outcome of the interaction were collected. Time spent is reported in three ways: (1) mean time involved in these interactions, (2) mean time spent relative to the physician's time spent seeing patients that week, and (3) mean time spent relative to the number of patients on the physician's panel. Linked interactions were grouped into episodes of care.

Results: Data were obtained from 9 fellows and 7 attendings for a total of 27 physician-weeks, representing 68% of ambulatory sessions for eligible physicians. Data consisted of 475 discrete interactions representing 300 episodes of care involving 231 patients. Mean interaction duration was 6.38 minutes (S.D. 7.36, range 0.5–120). Interactions were significantly longer when they involved the patient or family vs. all others (7.31 vs. 5.52 mins, $p=0.008$), and when temporally unrelated to an office visit (6.92 vs. 5.30 mins, $p=0.02$). There were no significant differences between fellows and attendings (6.43 vs. 6.27 mins, $p=0.82$), interactions involving patients with and without dementia (6.98 vs. 5.88 mins, $p=0.11$), and with physician's own patients vs. coverage (6.60 vs. 4.60 mins, $p=0.06$). Physicians spent, on average, an additional 18.7 minutes performing care coordination per 30 minutes of seeing patients in the office. Physicians spent 1.85 minutes performing care coordination per patient on the physician's panel per week. Episodes involving care coordination or counseling were statistically significantly longer in duration than those involving acute issues (22.8 vs. 12.8 mins, $p<0.05$). 36% of episodes involving acute issues resulted in medication use, 27% in an office visit, and 9% in a referral to another physician. 33% of interactions occurred within 1 week of an office visit. Of these, 58% followed the office visit, 34% preceded the visit, and 8% occurred on the same day. 78% of interactions were telephonic, 8% electronic, and 8% face-to-face. 24% of interactions took place with the patient, 24% with the family, 12% with another MD or NP, and 12% with a visiting nurse.

TABLE

Effect of "Low" and "High" Na Diet on Serum and Urine Electrolytes

Serum aldosterone (ng/dL)	n	Serum Na, mEq/L	Serum K, mEq/L	Urine Na, mEq/L	Urine K, mEq/L	
Low Na	5	133.8 ± 1.6	4.7 ± 0.2	0*	243.7 ± 50.4	75.6 ± 21.8
High Na	3	141.8 ± 2.3	4.7 ± 0.4	78.6 ± 3.8	263.3 ± 50.6	8.9

All results are expressed as means ± SE. n refers to the number of animals studied. * $p< 0.05$ compared to "High Na."

Conclusions: Geriatricians spent 18.7 minutes in nonreimbursable clinical interactions for every 30 minutes of seeing patients in the office. For a full-time geriatrician (16 visits/day over 5 days/week) this translates into an extra 25.0 hours of nonreimbursable clinical work/week. At least two-thirds of the interactions in this study were not temporally associated with a billable office visit. Episodes involving care coordination and counseling may span several interactions totaling over 20 minutes.

Barriers to Caring for Chronic Hepatitis C in HIV ("Co-infected") Patients. B. Forsyth and D. Fishbein. Mount Sinai School of Medicine, New York, NY.

Background: Chronic hepatitis C virus (HCV) is highly prevalent in HIV patients. Although end-stage liver disease (ESLD) is the leading cause of morbidity and mortality in hospitalized HIV patients, the majority of co-infected patients are not receiving HCV treatment. In this study we examine *provider* barriers to HCV treatment in HIV.

Methods: Anonymous surveys were distributed to all health care providers attending the International AIDS Society meeting in NYC in October 2005. The surveys contained knowledge, attitude and practice questions regarding co-infection.

Results: Of the 505 received surveys 244 (48%) were completed. The respondents were primarily nurse practitioners (NP) or physician assistants (PA) (29%), and physicians (55%); mean age was 45.3 ±10 with a median practice experience of 14 years. Half the providers self-reported referring <25% of their patients for HCV treatment. And 52% of providers report NOT *referring* for HCV treatment as often as they think they should, while 42% report NOT *initiating* HCV treatment as often as they think they should. Both groups cite "Patient does not want treatment" among their top three reasons. Physicians were significantly less likely than NPs/PAs to *refer* for this reason (OR 0.23; CI 0.09–0.59), however there was no difference between these groups in *initiating* treatment. Of those who DID *refer and initiate* as often as they thought they should, "we have an easy referral process" and "the risk of ESLD outweighs the risk of not treating," were among the most cited reasons. Many providers are not treating HCV themselves (69%), but would be willing if they had appropriate training (58%) and time and resources (66%).

Conclusions: Many HIV providers report discomfort in treating HCV without a referral. However, with additional training, resources and time they would likely increase their treatment rates. A significant barrier to the provision of HCV treatment is provider perception that patients themselves do not want treatment. Further exploration of this barrier is recommended to increase the percentage HIV patients receiving HCV care.

Dyspnea and Chylous Pleural Effusion in a 50-Year-Old Female. J. Freedman. Mount Sinai School of Medicine, New York, NY.

A 50-year-old woman was admitted to the hospital with dyspnea and a large right-sided pleural effusion which proved to be chylous. Further investigations led to a diagnosis of pulmonary lymphangioleiomyomatosis (LAM), a rare debilitating disease usually seen in women of childbearing age. Pulmonary LAM is characterized by peribronchial, perivascular, and perilymphatic non-neoplastic proliferation of smooth muscle cells. These changes are associated with recurrent spontaneous pneumothorax, pulmonary hemorrhage, chylous effusions, bronchial cyst formation, and progressive loss of lung function. In addition, there is an absence of associated inflammation or organized fibrosis with the predominant finding being numerous thin-walled cysts throughout both lungs. This patient's case is unusual in that she was post-menopausal upon presentation with a relatively short duration of symptoms prior to diagnosis. The case is presented in full, followed by a review of the available literature on pulmonary LAM focusing on differential diagnosis, radiologic and pathologic findings, clinical course, and management.

Translational Regulation of Gene Expression of NPM-ALK Kinase of Anaplastic Large Cell Lymphoma. K. Funato, N. Haq, Y. Sun, J. Chen, G. Khitrov, W. Zhang and D.W. Sternberg. Division of Hematology and Oncology, Mount Sinai School of Medicine, New York, NY.

NPM-ALK is an activated tyrosine kinase generated by the t(2;5)(p23;q35) chromosomal translocation associated with 50% of anaplastic large-cell lymphoma. Nucleophosmin-anaplastic lymphoma kinase (NPM-ALK) is known to play a causal role in the generation of hematopoietic neoplasia, and it has a multiple tyrosine residues that can bind to signaling proteins. We have found that expression of NPM-ALK regulates mediators of translational initiation, such as mTOR, S6K1, and 4E-BP1. These findings stimulated our hypothesis that NPM-ALK promotes neoplasia by altering the partitioning of specific mRNAs to polysomes and hence regulates the translation of specific mRNA molecules. In this study, we generated Ba/F3 murine hematopoietic cells transduced with a kinase-active NPM-ALK or a kinase-deficient NPM-ALK mutant (K210A). Our goal was the determination of the global profile of polysome-associated mRNA regulated by NPM-ALK kinase activity. We purified polysomal and total RNA from cell lysates, and we assessed the global profile of gene expression using Affymetrix mouse genome microarrays. Although we found little difference in total mRNA levels, we identified 286 genes altered significantly in the polysomal mRNA fractions. These included several of immediate interest to the pathogenesis of hematopoietic neoplasia. For example, Lyl1 or Tal1 are genes both associated with poor prognosis in T-cell acute lymphoblastic leukemia, and each of the respective mRNA's was enriched in the polysomal RNA fraction of cells with kinase active NPM-ALK. Our findings demonstrate the feasibility of assessing NPM-ALK-regulated gene expression through translational initiation, and these results suggest that polysome partitioning of mRNA species might be a locus of gene regulation in NPM-ALK-derived neoplasia.

Macrophage Phagocytosis of Apoptotic Cholangiocytes *in vivo* Is Impaired in PBC. J.Garber. Mount Sinai School of Medicine, New York, NY.

Introduction: Animal models suggest impaired macrophage phagocytosis of potentially immunogenic apoptotic cells plays a role in autoimmune disease. The consequent increased phagocytosis of apoptotic cells by dendritic cells can be pro-immunogenic under inflammatory conditions. Most primary biliary cirrhosis (PBC) patients have a quantitative decrease in phagocytosis of apoptotic cells by cultured monocyte-derived macrophages.

Aims: (1) To examine macrophage expression and function of CD14 and complement receptor 3 (CR3), receptors known to be involved in internalization of bound apoptotic cells. (2) Identify the cell types involved in apoptotic cholangiocyte phagcoytosis *in vivo* in normal controls and patients with PBC, primary sclerosing cholangitis (PSC), and mild acute rejection post-liver transplantation.

Patients and Methods: Blood was collected from 5 AMA+ PBC patients (stage 1–2) and 5 healthy controls, matched for age and gender. Isolated monocytes were cultured for 5 days in serum-free medium or medium plus 10% fetal calf serum. On day 5, the monocyte-derived macrophages were co-cultured with apoptotic human salivary gland epithelial cells previously stained with carboxy-fluorescein succinyl ester (CFSE). After 2 hours, non-adherent cells were removed, pelleted, and the supernatant was collected. Adherent cells were stained with mAbs against CD14 and CD11b (CR3) and subjected to flow cytometry. For immunohistochemistry, liver sections prepared from paraffin-embedded, formalin-fixed early stage biopsy specimens (5 for each diagnosis) were stained with mAb against either CD68 (expressed by macrophages and dendritic cells), CD163 (macrophages only), or CD83 (activated dendritic cells only) and counterstained with hematoxylin.

Results: Phagocytosis of apoptotic cells was significantly impaired by 35–70% in each PBC patient relative to controls. In normal controls, CD11b and CD14 expresssion were unaffected by phagocytosis of apoptotic cells. In the PBC patients, CD11b, not CD14, surface expression decreased significantly (>50%) following phagocytosis of apoptotic cells in both the presence and absence of serum. Immunohistochemical staining revealed CD68+, CD163-, CD83+ cells (dendritic cells) crossing the basement membrane and surrounding 80–90% of apoptotic cholangiocytes in the PBC biopsies. Apoptotic bodies were also observed within the cytosol of cholangiocytes and detached from the basement membrane. In the mild rejection biopsies, CD68+, CD163+, CD83- cells (macrophages) were most frequently observed surrounding the apoptotic cholangiocytes (70–85%). Too few apoptotic cholangiocytes were observed in the PSC and normal biopsies for analysis.

Conclusion: Macrophage phagocytosis of apoptotic cholangiocytes *in vivo* is decreased in PBC compared to mild rejection and may be due to CR3 dysfunction.

Indefinite Anticoagulation for Pulmonary Embolism in the Elderly: Benefits and Risks Forecasted by Decision-Tree Analysis and Markov Modeling. J. Haspel. Mount Sinai School of Medicine, New York, NY.

Treatment of venous thromboembolism (VTE) in the elderly represents a unique situation where the benefits and risks of anticoagulation are difficult to balance. This is particularly true with respect to pulmonary embolism (PE), which has a heightened recurrence rate and is more likely to re-present fatally. However, elderly individuals are also more likely to suffer bleeding complications and are at increased risk for falls that can lead to intra-cranial hemorrhage (ICH). To better understand the risks and benefits of treating idiopathic PE in elderly, fall-prone patients, this project utilized decision analysis to compare indefinite anticoagulation with coumadin to finite anticoagulation in the treatment of this disorder. Both Decision-Tree and Markov simulation methodologies were employed to forecast clinical outcomes, such as total survival, event-free survival, QUALY score and death, out to 5 years. The results suggest a favorable profile for indefinite anticoagulation with an ARR of 3.5% ± 0.15 for total survival, 20% ± 1.1 for event-free survival, and an average gain of 146 ± 18 QUALY-days by 5 years. The benefits of continued coumadin use increased progressively with time. Both Decision Tree analysis and Markov modeling produced similar results. Sensitivity analysis suggested that the ARR for total survival was sensitive to variations in several rates, including PE recurrence rate off coumadin (point of equivalence ~3%), GIB rate on coumadin (point of equivalence ~10%), and yearly all-cause mortality (point of equivalence ~10–20%). However, event-free survival more robustly favored long-term coumadin, even with PE recurrence rates as low as 1%, yearly all-cause mortality as high as 50%, and yearly all-cause hospitalization rate as high as 40%. Taken together, the data suggests that elderly, fall-prone patients who have had an idiopathic PE would benefit from indefinite anticoagulation compared to a finite course of 6-12 months. While elderly, frequently falling patients have a higher bleeding risk than younger patients, this is outweighed by the reduction in the rate of recurrent VTE and its complications. However, for sub-groups of patients who are known to have significantly lower PE recurrence rates (such as women or patients with total thrombus resolution) or patients with significantly heightened bleeding risks (such as cirrhotic patients), finite courses of coumadin may produce an equivalent benefit to long-term therapy.

BTNL-2 Gene Variation—A Potential Association with Sarcoidosis. J. Hsieh. Mount Sinai School of Medicine, New York, NY.

Sarcoidosis is a multiorgan granulomatous inflammatory disease of exaggerated cellular immune response. Although the exact pathogenesis of sarcoidosis remains unclear, familial aggregation studies have demonstrated a significant genetic component. Previously identified by single nucleotide polymorphism (SNP) scan, a single SNP (rs2076530; G/A) in the butrophylin-like 2 (BTNL-2) gene has been strongly associated with sarcoidosis in a white German population and to a lesser extent in African Americans. BTNL-2 is a member of the immunoglobulin gene family and is related to the B7 co-stimulatory receptor, although its exact function is unknown. Optimal T-cell activation involves antigen binding to the T-cell receptor and additional co-stimulatory interactions such as the binding of CD 28 expressed on T-cells to B7 on antigen presenting cells (APCs). rs2076530 introduces a frameshift and premature termination of BTNL-2. We propose that this truncated form of BTNL-2 lacks the transmembrane domain, rendering it incapable of inserting into the plasma membrane of APCs and turning off activated T-cells *in situ*. We are currently investigating BTNL-2 protein expression in APCs derived from both cell culture and from human buffy coat samples. These cells will be cultured with various cytokines of known importance in sarcoidosis and other immune-stimulating agents such as LPS. The time course of induction and relative abundance of various BTNL-2 isoforms will be assessed by RT-PCR, northern, and western blot analysis. We hypothesize that in controls, inflammatory cytokines will increase BTNL-2 cell-surface expression so it may participate in the down-regulation of activated T-cells. In sarcoidosis patients with the BTNL-2 gene variant, we propose that APCs expressing the truncated form of BTNL-2 will be unable to express the receptor on the cell surface and thus will be unable to down-regulate activated T-cells, resulting in the exaggerated T-cell response seen in sarcoidosis.

Case Report of Adult Onset Macromastia and Polymastia. L. Huang. Mount Sinai School of Medicine, New York, NY.

Background: While carcinogenesis of the breast has been extensively studied, the role of benign breast hyperplasia in understanding breast development and differentiation has not been as well described.

Objective: We describe an unusual case of adult onset benign polymastia and macromastia. Our goal was to investigate the pathogenesis of this anomaly by searching for growth factor over/under expression that may be leading to abnormal breast tissue growth.

Methods: In this study, we analyzed the expression of growth factors that have been implicated in breast development including progesterone receptor, ER-alpha, ER-beta, IGF1, IGF1-R, aromatase receptor (AR), TBG-B, TGF-B receptor, and SMAD by immunohistochemistry in paraffin-embedded sections of our patient's native and ectopic breast tissue. Positive findings were then compared to normal controls. Negative findings were not compared to controls.

Results: We found positive staining for AR, IGF-1, and IFG1-R in the patient's tissue. In addition, we found that expression of these factors in the patient's ectopic breast was greater when compared to controls.

Conclusion: While our results are inconclusive as to the definitive pathogenesis of our patient's condition, further investigation in benign breast hyperplasia may yield information as to treatment modalities for our patient, as well as new insight into breast development and differentiation.

Standardized Uptake Value of Stage 1 Nonsmall Cell Lung Carcinoma, a Predictor of Prognosis after Surgical Resection? A.S. Teirstein, A.M. Huysman, S. Swanson, D. Krellenstein, J. Machac, and J. Gil. Mount Sinai School of Medicine, New York, NY.

Background: The overall 5-year survival rate for nonsmall cell lung carcinoma (NSCLC) is only 14%. (Ahuja et al.). Although stage 1 patients have the best prognosis for surgical cure, the post-surgical recurrence rate has been reported as high as 35%. (Naruke et al.) The International Adjuvant Lung Cancer Trial Collaborative Group concluded that cisplatin-based chemotherapy improves survival among patients who have undergone complete resection of NSCLC. (IALT Collaborative Group) The intensity of radio-labeled 18F-fluoro-2-deoxy-glucose (FDG) uptake, a measure of increased glucose metabolism recorded as a standardized uptake value (SUV) on positron-emission tomography (PET) scans, has been correlated with the growth rate and proliferative capacity of NSCLC. (Duhaylongsod et al.) The goal of this study was to determine whether the SUV of a tumor on PET predicts prognosis after surgical resection of stage 1 NSCLC and may identify a subgroup of stage 1 NSCLC patients who would benefit from adjuvant treatment.

Methods: A retrospective review of patients who underwent surgical resection of stage 1 NSCLC and had FDG-PET scanning performed preoperatively was undertaken, at The Mount Sinai Medical Center, NYC. The records of 43 patients ranging in age from 53–90 years, and including 32 stage 1A tumors and 13 stage 1B tumors were analyzed. The SUV and size of the tumors were correlated with postoperative recurrence over a follow-up period of at least two years (range of 7–80 months).

Results: The mean SUV of the nodules was 5.62 g/mL ± 4.62 (1–21.64 g/mL). Eleven (24%) of the 45 tumors recurred during follow-up. In this sub-group of patients, the mean SUV was 5.55g/mL ± 4.68 (0–14.4 g/mL). This was not significantly different than that of the 45 tumors that did not recur during the follow-up period. In this sub-group of patients without recurrence, the mean SUV was 5.62 g/mL ± 4.69 (0–21.64 g/mL). Amongst tumors that recurred, the mean size was 2.94 cm (1.0–5 cm). Amongst those that did not recur, the mean size was 2.00 cm (0–5 cm).

Conclusions: SUV was not indicative of prognosis of surgically resected stage 1 lung cancers in this study population. Recurrence was more common in larger tumors but there was a large overlap in size between recurrence and no recurrence. The small size of stage 1 tumors may inherently limit the utility of SUV as a prognosticator. We propose that currently, indices of prognosis must comprise multiple factors, including SUV, size, cell type, and molecular biology.

Barriers to HIV Testing in a Large, Urban Academic Medical Center. C. Jain[1], J. Shin[1], C. Wyatt[1], F. Wallach[1], R. MacKay[1], and S. Jones[2]. [1]Mount Sinai School of Medicine, New York, NY and [2]Cornell University Medical Center, New York, NY.

Background/Objectives: Despite the 1993 CDC recommendation for routine, voluntary HIV testing in communities with an HIV prevalence >1 %, up to 40% of patients are still diagnosed with CD4 counts less than 200. Patients have come into contact with the health care system anywhere from 5–11 times prior to diagnosis, representing missed opportunities for early diagnosis and intervention. New York City remains the epicenter of the HIV/AIDS epidemic in the United States. This study was designed to better understand physician barriers to HIV testing in a large, urban New York City hospital.

Methods: Surveys were distributed to 137 Internal Medicine residents and 47 General Internal Medicine attendings from June 16–August 10, 2005. The survey response rate was 64%.

Results: Internal Medicine Residents reported that they ordered a median of 5 HIV tests over the prior year, while General Internal Medicine attendings reported ordering a median of 8 HIV tests. 41% of residents and 84% of attendings were prompted to order an HIV test if the patient was

MSM. 64% of residents and 81% of attendings were prompted to order an HIV test if the patient had heterosexual contact with an HIV positive person. 96% of residents and 94% of attendings reported that they were comfortable discussing sexual behavior and HIV status; however, only 54% and 81%, respectively, reported initiating risk behavior discussions. More than half of attendings only discussed sexual activity at specific events, and only 10% of attendings reported that they routinely ask about reasons for engaging in risk behaviors. Primary barriers to discussing risk behaviors identified by all respondents included (1) lack of time, (2) more important priorities, and (3) language barriers. 65% of General Internal Medicine attendings and 70% of Internal Medicine residents reported that an intake questionnaire would help facilitate risk behavior discussions.

Conclusion: Physician barriers to HIV testing exist in a large, urban academic medical center. While physicians reported feeling comfortable discussing risk behaviors, time constraints appear to prevent them from translating this into clinical practice. Routine, voluntary HIV testing should be incorporated in large, urban medical settings to avoid missed opportunities to impact the HIV/AIDS epidemic.

Doppler Tissue Systolic Wave Velocity Time Integral, a New Measure of Myocardial Performance.

S.G. Jawetz, L.B. Croft, and M.E. Goldman. Mount Sinai Medical Center, New York, NY.

Background: Derivatives of echo-Doppler can assess systolic and diastolic function. The Tei index is a load independent measure of myocardial performance, but requires multiple precise measurements, thereby limiting its general applicability and accuracy. Tissue Doppler imaging (TDI) has primarily been used to measure diastolic function. However, TDI also includes a systolic wave form (S-wave) that indicates total systolic myocardial displacement.

Objective: To determine if measures of the S-wave could serve as a surrogate of the Tei, we correlated the TDI S-wave with the Tei index, and two-dimensional left ventricular function (LVF).

Methods: We blindly, digitally measured the Tei index [(isovolumic contraction + isovolumic relaxation)/ejection time], S-wave peak velocity, and S-wave velocity-time integral (S-VTI) in 154 random patients' transthoracic echocardiograms. The patients were divided into two groups based on normal or abnormal LV systolic function and were heart rate and blood pressure matched.

Results: The S-VTI correlated with the Tei index ($r = 0.63$, $p<0.0001$). An S-VTI of $0.015m^2$ had a sensitivity of 69% and specificity of 90% to detect an abnormal/normal Tei index. While the S-VTI correlated with the peak S-wave velocity ($r =0.79$, $p<0.0001$), the peak S-wave velocity had a poor correlation with the Tei index ($r=0.29$, $p=0.0002$). The S-VTI differentiated patients with normal LVF vs. those with moderate or severe LV systolic dysfunction. The sensitivity and specificity of the S-VTI for detecting LV dysfunction was 51% and 96%, respectively; similar to the Tei index (48% and 93%, respectively).

Conclusion: The S-wave VTI is a simple, single measurement of myocardial performance with an excellent correlation with the Tei index.

Mutational Evaluation of NPM-ALK Signal Transduction in the Pathogenesis of Non-Hodgkin Lymphoma.

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The t(2;5)(p23;q35) chromosomal translocation juxtaposes the nucleophosmin (NPM) gene with the anaplastic lymphoma kinase (ALK) coding region, and the resulting fusion tyrosine kinase is known to mediate the pathogenesis of some forms of non-Hodgkin lymphoma. We have a limited understanding of signaling pathways that mediate lymphomagenesis driven by NPM-ALK expression. NPM-ALK interactions with signaling proteins are facilitated by protein tyrosine phosphorylation, which binds proteins that contain Src-homology-2 (SH2) or phosphotyrosine binding domain (PTB) motifs. In an effort to identify signaling intermediates that bind NPM-ALK, we tagged the NPM-ALK fusion kinase with the FLAG motif and expressed it in the Ba/F3 hematopoietic cell line. However, we were unable to identify specific interactions on a global scale using anti-PTyr immunoblot or silver staining methods. We speculate that many of the protein-protein interactions are either of low stoichiometry or are transient. In a second effort, we generated a series of Y-to-F substitution mutations within the NPM-ALK kinase. The NPM-ALK variants were used to assess the activity of signaling pathways that might promote cell survival and proliferation. STAT3 is a transcription factor that is known to play a critical role in NPM-ALK-driven lymphomagenesis. We found that a carboxy-terminal triple mutant (Y461F, Y567F and Y644F) attenuates STAT3 activation. Moreover, mutation at these sites impairs the cytokine-independent outgrowth of the Ba/F3 hematopoietic cell line. We also found that NPM-ALK could activate the ERK and S6K1 serine/threonine kinases. However, engagement of these downstream signaling molecules could not be localized to a discrete region within NPM-ALK, and we speculate that NPM-ALK signaling through ERK and S6K1 is mediated by promiscuous protein-protein interactions at multiple sites within NPM-ALK. Currently, we are correlating these findings with translational control of gene expression. In conclusion, we find that the domain requirements for STAT3 activation, but not ERK or S6K1 activation, are constrained within the carboxy terminal region of NPM-ALK fusion protein.

Role of the Ubiquitin-Like Protein FAT10 in Renal Epithelial Apoptosis.

J-Y Kim. Mount Sinai School of Medicine, New York, NY.

Background: FAT10 is upregulated in several malignancies (particularly hepatocellular carcinoma), autosomal dominant polycystic kidney disease (ADPKD), and HIV–associated nephropathy (HIVAN). In all of these conditions, there is dysregulation of cellular proliferation and apoptosis. While FAT10 is demonstrated to cause proteosome-dependent apoptosis in human and murine cell lines in vitro, its function *in vivo* remains unclear. We have previously shown that FAT10 is a critical mediator of HIV-induced apoptosis of kidney cells. However, it is not known whether FAT10 mediates apoptosis due to other proapoptotic stimuli.

Hypothesis: FAT10 is an important mediator of apoptosis in renal epithelial cells exposed to the staurosporine, an inducer of apoptosis.

Methods: Measurement of FAT10 protein expression: HK-2 cells (human proximal tubular kidney cells) were treated for 5 hours with 0.25 μM staurosporine, a chemical known to induce apoptosis via protein kinase inhibition or DMSO (control). Cells were harvested using M-PER protein extraction reagent (Pierce). Insoluble protein fractions were resolublized in 1% SDS and analyzed be western blotting using rabbit anti-FAT10 affinity purified antibodies.

Analysis of subcellular localization of FAT10: HK2 cells were grown on type 1 collagen-coated coverslips (rat tail collagen, BD Biosciences). Cells were incubated with staurosporine of DMSO control as above and incubated with Mitotracker Red CMXRos for 15 minutes prior to paraformaldehyde fixation. Cells were stained with an affinity purified FAT10 antibody followed by Alexafluor-488 goat anti rabbit antibody secondary antibody, and mounted with DAPI-containing media.

Quantitation of Apoptosis: To determine if inhibition of FAT10 is able to prevent staurosporine induced apoptosis, we transduced HK2 cells with 2 different FAT10 lentiviral shRNA vectors or control shRNA prior to incubation with staurosporine or DMSO. TUNEL staining was performed to assess apoptosis in all cell populations. Tunel staining was then done in each cell population using the DeadEnd TUNEL staining kit (Promega) and quantified by counting 10 high-power fields per slide.

Results: Western blotting demonstrated a 3.4-fold increase in FAT10 expression in the staurosporine treated cells compared to cells treated with DMSO when normalized with a loading control. Immunocytochemical staining for FAT10 revealed some colocalization with mitochondria and minimal nuclear staining. FAT10 expression was increased in cells treated with staurosporine. There was a suggestion of increased colocalization of FAT10 with mitochondria in staurosporine treated cells. TUNEL staining demonstrated increased apoptosis in the cells treated with staurosporine, but there was no difference in apoptosis observed in cells transduced with shRNA vectors.

Discussion: FAT10 expression was upregulated after treatment of cells with staurosporine and may traffic preferentially to mitochondria after staurosporine treatment. However, knockdown of FAT10 using shRNA did not prevent apoptosis. Additional studies are required to elucidate the mechanisms of FAT10 subcellular localization and function and its role in epithelial apoptosis.

Depressed Patients Are Less Likely to Follow Recommended Risk Reducing Behaviors after Acute Coronary Syndromes.

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Background: The persistence of depressive symptoms after hospitalization is a strong risk factor for mortality after acute coronary syndromes (ACS). Poor adherence to secondary prevention behaviors may be a mediator of the relationship between depression and increased mortality. We aimed to determine whether rates of adherence to risk reducing behaviors were affected by depressive status during hospitalization and 3 months later.

Methods: We enrolled 560 post-ACS patients at 3 university hospitals within 7 days of their coronary event. 492 (88%) patients completed follow-up at 3 months. We used the Beck Depression Inventory (BDI) to assess depressive symptoms at hospitalization and 3 months later. BDI <10 indicates symptoms of at least mild to moderate depression. We assessed adherence to risk-factor modification behaviors by patient self-report at 3 months. We used $\chi 2$ to compare differences in adherence among 3 groups: patients who were never depressed (BDI < 10 at hospitalization and at 3 months); patients whose depressive symptoms remitted (BDI ≥ 10 at hospitalization and BDI < 10 at 3 months); and patients with persistent symptoms of depression (BDI ≥ 10 at hospitalization and at 3 months). Multivariate logistic regression was used to calculate adjusted odds ratios controlling simultaneously for pre-specified confounders.

Results: The mean age was 61 years (range 32–93): 41% were female, 11% were Hispanic, and 13% were Black. Among patients who had symptoms of depression during hospitalization, 49% had persistent symptoms at 3 months and 51% had symptoms that remitted. Compared with persistently nondepressed patients, persistently depressed patients reported lower rates of adherence ($p<0.05$) to quitting smoking, taking medications, exercising, and attending cardiac rehabilitation. There were no significant differences in adherence between remittent depressed and persistently nondepressed patients (Table). We next used logistic regression to determine unadjusted and adjusted odds of adhering to recommended behaviors by depression status. Compared with persistently nondepressed , persistently depressed patients reported lower rates of adherence to quitting smoking (adjusted OR 0.23, 95% CI 0.05–0.97), taking medications (adjusted OR 0.50, 95% CI 0.27–0.95), exercising (adjusted OR 0.57, 95% CI 0.34–0.95), and attending cardiac rehabilitation (adjusted OR 0.5, 95% CI 0.27–0.91). Again, there were no significant differences between remittent depressed and persistently nondepressed patients.

Conclusions: Persistently depressed patients were less likely to adhere to behaviors that reduce the risk of recurrent ACS. Differences in adherence to these behaviors may explain in part why depression predicts mortality after ACS.

TABLE

Adherence Behaviors According to Depressive Status

Behavior	Never Depressed	Remitted Symptoms	Persistent Symptoms
Quit smoking	56%	67%	26%[2]
Took meds	87%	80%	71%[3]
Exercised	60%	55%	37%[2]
Cardiac rehab	37%	29%	18%[2]
Modified diet	72%	68%	65%

[2] Significantly different from the other 2 groups (<0.05).

[3] Significantly different from the persistently nondepressed group (<0.05).

Dysregulation of Hedgehog Pathway Signaling in Hepatocellular Carcinoma.

E.R. Lemmer. Y-B Chen, S. Yea, E. Wurmbach, M. Schwartz, G. Khitrov, A. Villanueva, G. Narla, S. Waxman, S.L. Friedman, and J.M. Llovet. Mount Sinai School of Medicine, New York, NY.

Hepatocellular carcinoma (HCC) is a major cancer worldwide whose incidence is rapidly increasing due to end-stage chronic hepatitis C virus (HCV) infection. There is no first line systemic treatment for advanced HCC. Knowledge of the signaling pathways involved in the initiation/progression of HCC will provide a rationale for the design of new molecular targeting agents. In order to characterize the changes in gene expression during the development of HCV-associated HCC, we collected samples from 78 HCV-cirrhotic patients undergoing surgical resection or liver transplantation for HCC. Gene expression of 56 candidate tumor pathway mRNAs were analyzed by real-time RT-PCR in lesions representing six progressive histologic stages (10 normal, 10 cirrhosis, 18 dysplastic lesions, 40 carcinomas) of HCC. Among these, key components of the hedgehog (Hh) signaling pathway, a tumor promoting pathway not previously studied in HCC, were, significantly dysregulated. We found that 24/40 (60%) of HCV-associated HCCs displayed two-fold or more upregulation of *Indian Hedgehog* (*IHH*, Hh ligand) expression compared to 1/28 (3.6%) of cirrhotic livers and dysplastic lesions ($p<0.001$). Concurrently, there was progressive loss of *Human Hedgehog Interacting Protein* (*HHIP*, tumor suppressor) expression with advancing stages of HCC. Human HCC cell lines Huh-7 and Hep-3B showed increased expression of key Hh pathway genes *IHH*, *PTCH*, and *GLI* (similar to very advanced HCCs), indicating Hh pathway activation. In contrast, Hep-G2 (human hepatoblastoma) cells lacked upregulation of Hh pathway genes, while expression of *HHIP* was completely absent in all three cell lines. Inhibition of Hh signaling by the natural alkaloid cyclopamine (dose 10 μM) resulted in decreased ^{3}H-thymidine incorporation by Huh-7 (by 23%) and Hep-3B (by 53%) cells, but not by Hep-G2 cells. In contrast, tomatidine (dose 10 μM)—a compound with a similar structure to cyclopamine but which lacks it inhibitory effects on Smo—had no effect on the proliferation of HCC cell lines. In conclusion, (1) Activation of the Hh pathway occurs in a subgroup of human HCV-cirrhotic HCCs; (2) Tumor growth in these patients appears to be ligand driven, and upregulation of *IHH* expression may be a critical molecular switch during the step-wise progression to HCC; and (3) Growth of human HCC cell lines displaying upregulation of Hh pathway gene expression appears to be inhibited by Hh pathway blockade.

Examining Physician Opioid-Prescribing Practices for Older Adults—A Retrospective Analysis.

E. Litrivis. Mount Sinai School of Medicine, New York, NY.

Background: Studies suggest that older adults are at high risk for undertreatment of pain and that they receive less analgesia for the same level of pain than their younger counterparts.

Objective: To examine physician practices of analgesic prescribing across different age groups.

Setting: Tertiary Care Academic Hospital.

Patients: A total of 1,115 patients, ages 18–75 years and older, enrolled in a study to examine a series of interventions designed to increase assessment and knowledge of pain. Patients were included if they were not taking opioids as an outpatient, did not have a history of liver disease, reported moderate to severe pain on the day of admission, and remained hospitalized for at least 72 hours.

Methods: Subjects were enrolled within 48 hours of admission to 9 matched medical and surgical units. Trained research assistants interviewed patients on a daily basis and asked them to rate their current pain, worst pain, and pain relief with analgesics on numeric rating scales. Patients were also queried as to opioid-related side effects including nausea, sedation, pruritus, and mental clarity.

Main Outcome Measures: Average pain at rest, worst pain over prior 24 hours, pain relief with analgesics, and prevalence of opioid related side effects.

Analyses: ANOVA and chi-square tests were used to compare continuous and discrete variables. Multivariate linear and logistic regression was used to examine outcome measures adjusting for covariates.

Results: There were statistically significant differences in the mean morphine equivalents administered amongst the different age categories and amongst surgical and medical pain management regimens overall. Amongst patients 18–49 years of age, the mean opioid dose required to achieve adequate pain relief was 50 morphine equivalents as compared to 21 morphine equivalents amongst patients 75 and older. Surgical patients in total received almost double the amount of morphine equivalents (186 versus 96) as compared to medical patients over a 5-day follow-up period. While older patients received less morphine equivalents than their younger counterparts, they overall achieved an equal amount of pain relief. Approximately 50% of all patients in each age category received adequate pain relief as defined as a pain score decrease from moderate—severe pain on hospital admission to mild—no pain by days 3–5.

Amongst all patients who reported moderate—severe pain at study entry and received an opioid, side effect profiles were also reported and recorded. No significant difference was observed among side effect profiles when comparing older adults to their younger counterparts.

Conclusions: Older adults require less analgesia for the same amount of pain relief as compared to younger adults without a significant difference in side effect profiles.

Phase I Study of Rituximab-Cyclophosphamide (R-CY) Stem Cell Mobilization and Rituximab-BEAM HDC with ASCT in Patients with Relapsed, Refractory or High Risk Intermediate Grade Non-Hodgkin's Lymphoma.

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The addition of rituximab to mobilizing regimens does not adversely affect collection of adequate numbers of CD34+ PBSC and may decrease tumor cell contamination. Prior administration of rituximab may sensitize lymphoma cells to chemotherapy, but its use with high-dose chemotherapy has not been studied. In this study, eligible patients had intermediate grade non-Hodgkins lymphomas (NHL) either primary refractory, relapsed or in CR-1 with an intermediate/high risk IPI score. Eight patients with a median age of 49 years (28–61) were enrolled in this study. Four patients had relapsed disease, chemosensitive to salvage in 3 patients, and untested in 1 patient. Two patients had primary refractory disease, chemosensitive to salvage. Two patients had intermediate-high risk IPI scores and were in CR-1. One patient in CR-1 declined to undergo transplant following stem cell collection. All patients had received rituximab previously. Stem cell mobilization was rituximab 375 mg/m^2 followed by CY 2 gm/m^2/day for 2 doses and filgrastim 10 ug/kg/d. High-dose chemotherapy consisted of rituximab 375 mg/m^2 on day-8, carmustine 300 mg/m^2 on day-7, etoposide 200 mg/m^2/d on days -6 to -3, cytosine arabinoside 200 mg/m^2 on days -6 to -3 (8 doses) and melphalan 140 mg/m^2 on day -2. Patients received filgrastim post transplant.

Results: The median CD34+ cell dose collected was 12.5 × 10^6/kg (1.1 – 33.2). There was one inadequate CD34+ cell collection requiring bone marrow harvesting which yielded 0.72 × 10^6/kg CD34+ cells. Engraftment of neutrophils and platelets occurred at a median of 8 and 11 days post transplant, respectively. Infectious complications included febrile neutropenia in one patient following mobilization and in 6 patients following R-BEAM. Transient grade I-II (common toxicity criteria) hepatic enzyme elevation occurred in 2 patients following R-CY. Following R-BEAM, 3 patients developed grade II-IV LFT elevation without evidence of VOD, which resolved. One patient developed moderate hemorrhagic cystitis which resolved. One patient developed bilateral pulmonary infiltrates of unknown etiology (BAL negative for organisms) which resolved. Immunoglobulin levels remained normal in two patients, but decreased in all other patients for up to a year post transplant. Peripheral blood flow cytometry and T cell subset analysis showed absent B cell populations, decreased CD4 cells and increased CD8 cells in all patients up to a year post transplant. Five patients are alive with no evidence of disease 381 – 676 days after transplant. Three of these patients developed PET positive lymph nodes that showed florid follicular hyperplasia on biopsy, with no evidence of lymphoma. Two patients had persistent disease following transplant. One patient underwent a non-myeloablative allogeneic transplant and died of progressive disease.

Conclusions: R-CY was well tolerated as a mobilization regimen and led to adequate stem cell collection. The addition of rituximab to the high dose chemotherapy regimen did not appear to increase the incidence of infections or peritransplant complications in this Phase I study. The effect on disease free survival, or the addition of rituximab to the collection and preparative regimens requires further investigation.

Assessing the Immunosuppressive Effects of 6MP/Azathioprine in IBD. L. Malter. Mount Sinai School of Medicine, New York, NY.

Background: Azathioprine/6 mercaptopurine (AZA/6MP) are immunomodulatory agents that are used for the treatment of immune mediated inflammatory diseases and transplant rejection including inflammatory bowel disease (IBD). In IBD, the indications for its use include disease refractory to treatment with 5ASA and steroids, as a steroid sparing agent, in conjunction with anti-tumor necrosis factor α mAb, or in the treatment of fistulizing Crohn's disease. The dose of AZA/6MP used in IBD is lower that that used to treat malignancy or transplant rejection where greater immunosuppression is required. The majority of studies evaluating the immunosuppressive effects of AZA/6MP have been conducted in patients taking higher doses. The goal of this study is to evaluate the effect of AZA/6MP on humoral and cellular immune responses in IBD patients, both *in vivo* and *in vitro*.

Methods: Twenty patients with Crohn's disease or ulcerative colitis diagnosed by colonoscopy and confirmed by biopsies or small bowel radiograph and non-inflammatory controls are studied prospectively following the initiation of 6MP/AZA therapy. Venous blood is obtained prior to starting 6MP/AZA and after 3 and 6 months of therapy. Lymphocyte counts, *in vitro* response to antigen (Candida and Tetanus) and mitogen stimulation (Con A, PHA, PWM), and total and IgG subclass immunoglobulins are determined. Response to pneumococcal, tetanus, influenza and Hemophilus influenza B vaccinations are analyzed as well. We analyzed values using stimulation indices to normalize lymphocyte proliferation in response to various stimuli.

Results: We are presenting an interim analysis of 17 patients recruited thus far. We initially compared the *in vitro* response to antigen and mitogens prior to receiving treatment in IBD patients vs controls. The patient response to all stimuli was comparable to controls confirming there was no baseline immunosuppresion in IBD patients. Following treatment, the response to PHA trended to be lower but the response to Con A and PWM remained stable. Similarly, the response to Candida and Tetanus was unchanged in the setting of 6 MP therapy. Lastly, the percent CD4 count was unchanged in treated patients.

Conclusions: The data to date support the contention that therapy with azathioprine/6 mercaptopurine, at doses used in the treatment of IBD, does not suppress systemic immune responses *in vitro*.

Serum Vascular Endothelial Growth Factor (VEGF) and Hepatocyte Growth Factor (HGF) Are Increased following Transarterial Chemoembolization (TACE) in Unresectable Hepatocellular Carcinoma (HCC). J.D. Schwartz, M.C. Marcotrigiano, Q. Zuo, and J.L. Gabrilove. Mount Sinai School of Medicine, New York, NY.

Background: TACE prolongs survival in unresectable HCC; tumor recurrence is nonetheless frequent and TACE is rarely curative. HCC is a vascular neoplasm in which aberrant cytokine pathways likely contribute to growth and angiogenesis. We sought to characterize the clinical course of HCC patients undergoing TACE and to determine potential association between TACE and levels of circulating VEGF and other cytokines.

Methods: We measured circulating VEGF, HGF, basic fibroblast growth factor (bFGF), tumor necrosis factor (TNF)-alpha, and transforming growth factor (TGF)-alpha in the serum of 38 patients undergoing TACE; cytokines were measured pre-treatment, and at days 1 and 2, and weeks 1, 2 and 4 following TACE. All patients were followed for HCC progression and survival.

Results: A total of 38 HCC patients underwent TACE. Median age was 57 (21 – 80); 30 patients were male; 30 had HCV-related liver disease; 34 had ECOG PS 0 – 1; 19 had Child-Pugh Class A liver dysfunction; median tumor diameter was 3.6 cm (1.3 – 9.6 cm); median number of tumors was 3; 8 patients had unifocal tumor and 14 had ≥ 5 tumors. Median time-to-progression was 7 months (range 1 – 40+), excluding 5 patients who died of progressive hepatic failure or complications secondary to TACE or liver transplant (OLT) within 6 months. Median overall survival (OS) was 12 months (range: 2 – 40+). Frequent toxicities included nausea (76%; 24% grade 3), pain (71%; 16% grade 3) and fatigue (68%); serious toxicities included grade 4 GI bleeding (5%), hemoperitoneum (3%) and jaundice (4%). Mean circulating VEGF was elevated from a baseline of 229 pg/mL (standard error (SE) 56) to 600 pg/mL (SE 166) at 1 week following TACE and decreased to baseline levels at 4 weeks. Serum HGF was elevated from baseline (1,712 pg/mL; SE 250) to 2,847 pg/mL (SE 523) at 2 days following TACE and also returned to baseline at 4 weeks. Serum bFGF, TNF-alpha and TGF-alpha were not significantly elevated from baseline following TACE.

Conclusions: TTP and OS vary widely in patients with unresectable HCC following TACE. Both HGF and VEGF are significantly elevated following TACE. We are currently investigating potential association between elevation of these cytokines and clinical features and outcomes.

Subspecialty Evaluation of Chronically Ill Patients with Suspected Immune Defects. A. Mehra[*], P. Sidi[#,**], J. Doucette[+], L. Estrella[**], and C. Cunningham-Rundles[**]. Mount Sinai School of Medicine, New York, NY.

Background: The diagnosis of primary immunodeficiency is suggested by illnesses including recurrent, unusual, or persistent infections. Since the diversity of defects and clinical presentations present a diagnostic challenge in large hospital populations, we devised a computer algorithm to identify such patients.

Objective: To determine the patterns of medical care rendered to patients with clinical features of immunodeficiency and assess utilization of pertinent sub-specialty clinics.

Methods: Using a validated algorithm based on disease codes from the International Classification of Disease (ICD-9), applied to Mount Sinai Hospital billing records, we identified all hospitalized patients, age 60 years or less who had been given two or more of 174 diagnoses of illnesses often associated with immunodeficiency. ICD codes were weighted for severity and expressed as a sum for admissions between 1/1/99 and 12/31/03; records of subjects with scores of 6 or greater were studied. Demographic and clinic attendance were assessed using billing records.

Results: The 296 computer-identified patients were 36% Hispanic and 27% African American with a median age of 13.3 years. Twenty-six percent live in the hospital's zip code; 75% receive primary care at Mount Sinai. Patients were hospitalized a median of 4.2 times (range 1 to 42). While 81% of the subjects had 402 episodes of pneumonia, only 169 subjects (55%) had ever received an evaluation from Allergy/Immunology or Pulmonary services.

Conclusion: Despite receiving primary medical care at one hospital, frequently hospitalized subjects with clinical features of immunodeficiency do not receive medical care in appropriate subspecialty clinics.

Identification of a Retrovirus in Human Breast Cancer. S.M. Melana, I. Nepomnaschy, M. Saskalian, H. Rojowsky, A. Abbott, J. Hasa, J.F. Holland, and B. G-T Pogo. Hematology / Oncology Division, Department of Medicine. Mount Sinai School of Medicine, New York, NY.

We have previously reported sequences homologous to the env gene of Mouse Mammary Tumor Virus (MMTV) but not to human endogenous retroviruses in 38% of the human breast cancers studied, yet they were absent from others human tissues (Wang et al, Cancer Res 1995, 55:5173). We have also found that normal breast tissue from env positive breast cancer patients was negative, suggesting that the sequences are of exogenous origin (Melana et al. Cl Cancer Res 2001, 7:283). The sequences were also expressed in most of the positive breast cancer specimens as detected by reverse transcriptase (RT) PCR (Wang et al. Cl Cancer Res 1998, 4:2565). Finally, the complete 9.9 Kb proviral sequence of an MMTV-like agent has been amplified and sequenced in two breast cancers (Liu, B. et al. Cancer Res 2001, 61:1754). Structural features of this provirus suggest that it is functional. We have looked for the presence of viral particles in primary cultures (MSSM cells) of env sequence positive tumors. The cells expressed Env proteins as shown by immunofluorescence and western blot. FACS analysis indicated that between 10–20% of the cells expressed the surface protein. Retroviral particles budding from cells as well as in particulate fractions from culture media were observed by electron microscopy. Particulate fractions also display reverse transcriptase (RT) activity and the presence of all viral genes as detected by RT-PCR. The RT activity peaked at densities characteristic of retroviruses in sucrose gradients. None of these properties were observed in similar studies with normal human mammary epithelial cells (HMEC) primary cultures or established normal breast cell line (MCF10F). Co-culture of MSSM virus-producing cells with HMEC, MCF10F, and B cells (Ramos) demonstrated transfer of viral sequences, as detected by PCR, and expression of Env proteins by western blot and FACS analysis in the recipient cells. Taken together, these findings support the identification of a human mammary tumor virus (HMTV) similar to MMTV in human breast cancer, which is able to infect human cells. Morphological cell transformation and tumorigenesis experiments are being performed.

The Frequency of *FAT10* Alleles in Renal Transplant Recipients. S.A. Mesher, C.M. Wyatt, B.T. Murphy, B. Schroppel, and M. J. Ross. Mount Sinai School of Medicine, New York, NY.

Background: Many factors affect outcome in renal transplant recipients, including genetic and environmental factors. FAT10 is a ubiquitin-like protein that has been shown to be upregulated in patients after infection with HIV-1, and is capable of inducing apoptosis in human renal tubular epithelial cells. Four distinct alleles of FAT10 have been identified (*FAT10*$^{a\text{-}d}$), with one allele (*FAT10*^{b}) noted to be more prevalent in patients with HIV associated nephropathy (HIVAN). We tested the hypothesis that particular *FAT10* alleles are associated with conditions leading to end stage renal disease (ESRD) and with renal transplant outcome.

Methods: The *FAT10* gene was amplified and sequenced from genomic DNA from 83 renal transplant recipients. Chi-square analysis was used to test the association between each FAT10 allele and several variables, including demographic data (race, sex), predisposing conditions (hypertension, diabetes, other disease), and transplant outcomes (total rejection episodes, fewer than 2 rejection episodes, and post-transplant creatinine clearance at 1 and 5 years). We also compared the prevalence of alleles (stratified by race) in our population with allele frequencies derived from a single nucleotide polymorphism (SNP) database (dbSNP, www.ncbi.nlm.nih.gov) using Fisher's exact test.

Results: A total of 83 DNA samples were analyzed (166 alleles) in 28 Caucasians, 22 African Americans (AA), and 28 Hispanics. Frequencies were calculated for each *FAT10* allele. Of 166 alleles, there were 102 alleles of FAT10^{a} (frequency 0.61), 38 alleles of FAT10^{b} (frequency 0.23), 0 alleles of FAT10^{c} (freq 0.0), and 26 alleles of FAT10^{d} (frequency 0.16). The FAT10^{b} allele was significantly associated with AA race ($p<0.001$). There was no statistically significant difference in predisposing conditions, transplant outcome or creatinine clearance at 1 and 5 years among the various groups. The prevalence of the *FAT10*^{c} allele in the transplant recipient cohort was significantly lower than has been reported in other cohorts of similar racial background ($p<0.0001$).

Conclusions: No association was detected between *FAT10* alleles and outcome after renal transplant in this study. We cannot rule out, however, that an association was missed due to our limited sample size. The absence of the *FAT10*^{c} allele was noteworthy, as published SNP data have shown its frequency in the general population to be 25% in Caucasians and 3% in Africans. The FAT10^{c} allele may be associated with resistance to chronic kidney disease, and further study should be undertaken looking for the allele in a chronic kidney disease population.

Internal Medicine Housestaff Experience with Interdisciplinary Team Work on the ACE Unit. R. Kellerman Miller, and E. Callahan. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Objectives:

1. Assess Mount Sinai Internal Medicine Housestaff ("Housestaff") attitudes toward and knowledge of interdisciplinary teams (IDT) and the roles of members of an interdisciplinary team.
2. Assess Housestaff experience with interdisciplinary teamwork.
3. Evaluate the effect of a 4-week rotation on the geriatric medical service towards the attitudes of Housestaff on interdisciplinary teamwork.

Description of Educational Project: Housestaff rotate for 4 weeks on the Acute Care for the Elderly (ACE) Unit and are expected to function as members of the IDT. Dedicated interdisciplinary rounds are scheduled daily and Housestaff are expected to attend two times per week. During their ACE orientation, Housestaff were given a description of their role in interdisciplinary rounds and principles of interdisciplinary rounds. Each rotation also included a 1/2-hour educational session with the geriatric nutritionist and physical therapist. Pre- and post-rotation surveys were distributed and collected by the authors.

Evaluation: At the start of their rotation, we used four-point Likert scales to assess Housestaff's attitudes toward IDT, knowledge of other disciplines, and previous experiences in IDT. At the end of their rotation, we asked similar questions. In addition, we asked if their attitudes changed after the four weeks.

Discussion: Preliminary results:

1. Pre-rotation attitudes were very positive overall. The higher-than-expected baseline signifies a change in the overall attitudes of Housestaff when compared to the Geriatrics Interdisciplinary Team Training (GITT) study (Leipzig, JAGS, 2002).
2. Prior to rotation, Housestaff reported greater knowledge of the roles/responsibilities of nurses/social workers versus nutritionist/physical therapists.
3. Most of the Housestaff had prior experience with IDT in medical school and residency.
4. ACE rotation had very little effect on the attitudes of Housestaff and their knowledge of IDT. Full results to be presented.

Conclusions: Housestaff are being trained in a manner more solicitous of interdisciplinary teamwork. They are therefore entering their post-graduate training with a more positive attitude toward such teamwork based on these experiences. We think that the ACE Unit rotation was not very influential in their attitudes because they began their rotation with a very positive attitude, only PGY 2 and 3 were expected to attend IDT rounds, and some of the structure of the rounds was lost due to changes in their rotation.

In the future, housestaff involvement with IDT could be incorporated into other educational methods such as role-plays and case based discussions, with accompanying "Team Assessment tools" in addition. focus groups with both the housestaff and other team members may help investigate different ways to improve housestaff experiences in an interdisciplinary teamwork.

Desmoid Tumors: Looking for a Cause and a Cure. F.P. Noto. Mount Sinai School of Medicine, New York, NY.

Desmoid tumors (DTs) are benign proliferation of fibroblasts which by virtue of their local aggressiveness and interference with the functioning of adjacent organs can produce significant morbidity and mortality. DTs are rare tumors with an incidence of 0.37 per 100,000 per year. DTs however occur in up to 20% of patients with familial polyposis syndromes, the genetics of which may offer a lead into the molecular pathogenesis of uncontrolled fibroblast proliferation disoders. The dysregulated expression of the beta-catenin gene has been associated with DTs and may offer a target for the development of therapeutic interventions. Currently, the standard treatment for DTs is surgical resection, but complete resections are rare and recurrences common. Other modalities which have been attempted include radiation therapy, noncytotoxic and hormonal therapy as well as cytotoxic chemotherapy. Cures with current treatment modalities are rare and the investigation of the cause of DTs may offer the best hope for a curative intervention in the future.

Cortistatin Modulates Immune Responses and Is Deficient in Lamina Propria Mononuclear Cells from Inflammatory Bowel Disease (IBD) Patients. S.J. Brown, Y. Zheng, P. Ponda, L. Mayer, K. Patel, and M. Babyatsky. GI Division and Shared Research Facility, Mount Sinai School of Medicine, New York, NY.

Background: Cortistatin (CST) is a novel neuropeptide, homologous to somatostatin (SST) in its receptor binding domain. Intestinal SST expression is decreased in IBD (Gastroenterology 1996; 110:A957) and SST has been ascribed immunomodulatory properties. New data indicates CST, and not SST, is actually expressed by cells of the human immune system (Dalm V, Clin Endo 2004; 60:625) suggesting CST may play a more significant role as an autocrine or paracrine immune regulator. We examined biopsies from ulcerative colitis and Crohn's colitis patients (n=9) and non-inflamed controls (n=18) for CST mRNA expression and determined the immunomodulatory effect of CST on macrophage hybridoma cells (clone-63) and Jurkat cells.

Methods: Lamina propria mononuclear cells were isolated and mRNA extracted. Q-PCR was performed using CST-specific primers with rps-11, β-actin and α-tubulin serving as housekeeper genes. Non-stimulated cell lines were treated with human CST-17 at 0.1 and 1 uM for 1, 4, and 16 hours. mRNA was harvested and RT-PCR for interleukin (IL)-12p40, IL-10, IL-13, interferon g (IFNg), IL-4, TGFB was performed using a MPCR kit (Maxim BioTech). Expression levels were determined relative to GAPDH housekeeper gene.

Results: Cortistatin expression was reduced in IBD samples with a mean value of 9.10 U (± 2.24 SEM) compared to 127.9 U (± 56.1 SEM) for normal controls (p=0.004 Mann-Whitney). This difference appeared to apply to both active and inactive disease and to both Crohn's and ulcerative colitis.

CST treatment of clone-63 cells led to a 1.6 – 4.1-fold inhibition of IL12p40 production. IFNg production was also inhibited up to 2.7-fold in a time and dose dependent fashion. A mild, 1.5-fold increase in TGFB production was also seen. CST treatment of Jurkat cells led to a 1.7-fold inhibition of IFNg production that was time and dose dependent. No significant change in the expression of other examined cytokines was detected.

Conclusions: We demonstrate for the first time that (1) CST expression is reduced in lamina propria cells from IBD patients and (2) CST displays immunomodulatory properties. Altered CST expression may contribute to the pathogenesis of IBD and CST may prove to be a novel therapeutic peptide.

Loneliness and Partner Status Are Associated with Poorer Adherence to Recommended Health Behaviors after Acute Coronary Syndromes. M. Paz-Yepes[1], N. Rieckmann[2], I. Kronish[3], M.M. Burg[4], J.E. Schwartz[5], and K.W. Davidson[4]. [1]Cardiovascular Institute, [2]Psychiatry, and [3]Medicine, Mount Sinai School of Medicine, New York, [4]Medicine, Columbia University, New York, NY; and [5]Psychiatry, Stony Brook University, Stony Brook, NY.

Social isolation predicts pathogenesis of coronary artery disease, possibly because of poor health behaviors. We previously reported that depression is associated with poorer health behaviors after an acute coronary syndrome (ACS). Here, we examined whether social isolation, defined by not having a partner and perceived loneliness, is associated with health behaviors independent of depression.

We enrolled 560 patients within 7 days of an ACS. A total of 492 patients (88%) completed follow-up at 3 months. Partner status, the UCLA loneliness scale (6-items), and the Beck Depression Inventory (BDI) were assessed at baseline. Self-reported health behaviors were assessed at 3 months. Patients without a partner (n=174, 35%) scored marginally higher on the UCLA scale than those with a partner (M=2.0, SD=0.7 vs. M=1.9, SD=0.5, p=0.13). Scores on the UCLA scale and BDI were moderately correlated (r=0.54, $p<0.001$).

After 3 months, patients without a partner were less likely to participate in cardiac rehabilitation (35% vs. 64%, p=0.01) or exercise (46% vs. 57%, p=0.03), and were more likely to smoke (15% vs. 8%, p=0.01). There were no group differences in self-reported medication adherence and diet change ($p>0.20$).

UCLA score was associated with decreased medication adherence (r=-0.21, $p<0.01$), lack of exercise (p=0.02), and a greater likelihood of smoking (p=0.02). Hierarchical regression analyses including age, gender, UCLA score, partner status and depression as predictors showed that both UCLA score and not having a partner, but not depression, were associated with smoking. Depression, but not UCLA score or partner status, was significantly associated with decreased likelihood of cardiac rehabilitation or exercise participation, and decreased medication adherence (all $p<0.05$).

These data suggest that social isolation, defined by not having a partner and perceived loneliness, should be considered when improvement in health behaviors is needed after acute coronary syndromes. Social isolation is associated generally with health-damaging behavior, whereas depression is associated with a decreased engagement in physical activity and medication adherence. Differential treatments may be implicated for socially isolated vs. depressed patients.

Efficacy of a Clinical Feedback Form in Improving Feedback in Medical Education. L. Peccoralo[1], K. Arbatova.[1], E. Friedman, L. Bensinger, and J. Koestler. Mount Sinai School of Medicine, New York, NY. [1]Co-first authors.

Introduction: Medical education literature highlights the distinction between the evaluation of clinical performance at the end of a clerkship and the feedback given by faculty to students throughout a clerkship. Feedback improves clinical skills and increases student self-awareness throughout medical education. In fact, it has been shown that the best educators consistently use feedback as part of their teaching. However, not all feedback is considered useful. Valuable feedback should include an assessment of a student's strengths and weaknesses and specific ways in which to improve clinical skills. Despite what we know about the importance of feedback, it is still lacking in quantity and quality throughout clinical education.

Hypotheses: We hypothesize that students are unsatisfied with the feedback that they currently receive in the third year. In addition, there are specific barriers to giving effective feedback that we can identify. Finally, we hypothesize that a written clinical feedback form will facilitate supervisors giving feedback in medical school clerkships at Mount Sinai School of Medicine (MSSM).

Methods: We first assessed satisfaction with and barriers to feedback using separate questionnaires tailored to students and their supervisors (residents). The first set of questionnaires were administered in July and August of 2005 and included specific questions regarding qualities of good feedback, satisfaction with feedback received or given, and barriers to adequate feedback. In order to improve feedback given in clinical clerkships we developed a concise clinical feedback form that students give to their supervisors throughout the third year clinical clerkships. The form is intended to be a guide for a feedback encounter between a student and his/her supervisor (usually a resident). The efficacy of the form will be evaluated by administering additional questionnaires to the students, residents, and faculty that used the forms. The study will be completed at the end of the 2005 – 2006 academic year.

Preliminary Results: Preliminary data demonstrates that there is a consensus between medical students' and residents' perception of the importance of feedback in clinical education. A large proportion of residents reported giving insufficient feedback, while a large proportion of medical students reported receiving inadequate feedback during their clerkships. Specific barriers to adequate feedback were noted by both medical students and residents. We will assess whether some of these barriers are addressed by our current intervention and hope to identify future interventions that will improve the quality of feedback for students at MSSM.

Medication Beliefs Predict Adherence to Inhaled Steroids in Inner City Asthmatics. D. Ponieman[1], J.P. Wisnivesky[1], H. Leventhal[2], and E.A. Halm[1]. [1]Mount Sinai School of Medicine, New York, NY, and [2]Rutgers, The State University of New Jersey, New Brunswick, NJ.

Background: Asthma morbidity, mortality, and health services utilization is highest among inner-city populations. Adherence to daily inhaled corticosteroids (ICS) therapy is the cornerstone of evidence-based asthma management. However, adherence is often suboptimal. Several domains of medication beliefs may influence adherence with ICS including beliefs about necessity/importance, concerns, self-efficacy, and regimen complexity, among others. This study sought to examine a range of medication beliefs and their association with adherence to ICS.

Methods: Detailed sociodemographic, clinical, and health belief data were collected in a prospective, observational cohort of inner city adults with persistent asthma in English and Spanish. Medication beliefs were based on Self-Regulation Theory and previously developed instruments. Beliefs about necessity related to importance of using ICS when symptomatic (SX) and when asymptomatic (ASX). Concern items related to worries about side effects and addiction. Other items include: "confidence in ability to use ICS (self-efficacy), and "how hard to follow your medication schedule (regimen complexity). Self-reported adherence to ICS was assessed using: (1) the Medication Adherence Reporting Scale (MARS), a validated, 10 item tool measuring overall adherence to ICS (Cronbach's alpha=0.83), and (2) questions about frequency of use of ICS when SX and when ASX. Associations between beliefs and ICS adherence was assessed using Spearman correlations and chi square tests. Multivariate (MV) analyses adjusted for other factors known to influence adherence (age, sex, and asthma severity).

Results: Of the 204 patients (Pts), mean age was 48 yrs, 60% Hispanic, 30% Black, and 20% completed the survey in Spanish. Overall, 10% had prior intubation, 57% prior asthma hospitalizations, and 71% had used oral steroids; 85% were prescribed ICS. Among these Pts, they reported using their ICS all/most of the time more often when having SX v. ASX (74% v. 68%, $p<0.0005$). In univariate analyses, medication adherence (MARS score) was associated with beliefs about the importance of using ICS when ASX, worries about addiction and side effects, confidence in using ICS, and regimen complexity ($p<0.05$). In MV models that adjusted for age, sex, and asthma severity, beliefs about importance of using ICS when ASX, worries about addiction, and confidence in using ICS remained significant predictors of medication adherence (MARS). In stepwise MV models that considered all beliefs together, beliefs about the importance of using ICS when ASX and confidence in using ICS were independent predictors of overall adherence adjusting for age, sex, and severity ($p<0.05$). As predicted by the conceptual model (in univariate and MV models), beliefs about the importance of use of ICS when ASX was correlated with use of ICS when ASX ($p<0.0001$), but not ICS use when SX ($p=0.3$). Similarly, beliefs about importance of using ICS when SX were associated with adherence when SX ($p<0.0001$), but not adherence when ASX ($p=0.5$). Greater worries about addiction to ICS were associated with less frequent use of ICS when SX and ASX ($p<0.005$).

Conclusions: Several key positive and negative beliefs about medications were associated with several measures of adherence to ICS. Eliciting and addressing these underlying beliefs may help improve adherence and outcomes. These potentially modifiable beliefs are promising targets for future asthma self-management interventions.

Simplified Insulin Drip Protocol for Patients with ACS Admitted to a Cardiac ICU. M. Ryan. Mount Sinai School of Medicine, New York, NY.

Objective: To assess the effectiveness of a simplified insulin drip protocol on patients admitted to a cardiac intensive care unit with symptoms of acute coronary syndrome.

Patients: This study is a case series of 14 patients admitted to the Mount Sinai Hospital Cardiac Care Unit from June through October 2005. All patients had either known diabetes or were found to have a plasma glucose of greater than 200 on admission to the CCU. The average age in the study group was 70.1 years with a range from 54 to 86.6 of the subjects were women and 8 were men. The study group included the following ethnicities: Caucasians, Asians, South Asians, African Americans and Hispanics. The average BMI in the study group was 28.4 (23 – 38) and the average baseline HbA1C was 8.57. The majority of patients also had hyperlipidemia and hypertension and 4 of the study patients were on hemodialysis for renal failure.

Methods: The insulin drip protocol was to be initiated in patients with diabetes or with blood glucose > 200 mg/dL admitted to the CCU within 48 hours of the onset of acute coronary syndrome. The goal was to maintain patients within a blood glucose range of 81 – 140 mg/dL. The initial rate of the insulin drip was determined by the patient's starting blood glucose level and the rate was adjusted based on repeat blood glucose measurements.

Results Of the 14 patients in the study, 9 reached the goal blood glucose range of <140 within 4 hours of initiation of the drip. The average blood glucose level for patients while on the drip was 156mg/dL. There were no incidences of significant hypoglycemia (defined as blood glucose <40mg/dl) in any patients during this study.

Conclusions: This simplified insulin drip protocol is effective in lowering and maintaining blood glucose levels and is very safe. Despite the common fear of hypoglycemia in patients on an insulin drip, its incidence in this small study was extremely rare.

A Patient Navigator (PN) in an Open Access Endoscopy (OAE) Program Facilitates Completion and Satisfaction with Screening Colonoscopy (SC) among Low-Income Underrepresented Minorities (URMs). S. Santos, L. Jandorf, S. Itzkowitz, A. Castillo, and J. Christie. Mount Sinai School of Medicine, New York, NY.

Background: African Americans and Hispanics have lower screening rates for colorectal cancer (CRC) than Caucasians. Organizational barriers such as lack of patient (pt) access to timely referrals, adequate follow-up and reminder systems have an impact on successful CRC screening. OAE is becoming more common in the United States. The advantages of OAE include shorter waiting times, better control by referring physicians over pt management for preventive services, and lower costs and inconvenience by eliminating an initial gastrointestinal consultation.

Aim: To assess pt satisfaction with the SC process in an OAE program.

Methods: Average risk, asymptomatic URMs from the primary care clinic at Mount Sinai Hospital were referred for SC through OAE. The majority of pts reside in East Harlem, a medically underserved community. The role of the PN included pt education, explanation of bowel preparation, scheduling appointments, assisting with transportation/escorts, and providing counseling and support to pts. After referral, the PN contacted each person to assess appropriateness for OAE and discuss the procedure and bowel prep. Two weeks after SC, pts were contacted by phone to conduct a 19-item patient satisfaction survey.

Results: From June–Oct 2005, 120 people completed their SC and 106 completed the pt satisfaction survey (response rate: 88%). 85% were female. 56% were Hispanic, 29% African-American and 11% Caucasian. The mean age was 56.2 (SD= 5.2). 84.2% stated that their primary care provider (PCP) adequately explained the reason for the SC. After contact with the PN, this rate increased to 92.1% ($p=0.02$). 34.9% of pts were extremely satisfied with their PCP's explanation of the bowel prep in comparison to 58.5% following the PN explanation ($p=0.00$). 83% were extremely satisfied or satisfied with PCP explanation of bowel prep versus 99.1% after PN explanation (p=NS). 94% of pts were extremely satisfied /satisfied with the SC procedure itself, and 89% were extremely satisfied/satisfied with the sedation during the procedure. Only 2% of pts were dissatisfied with the quality of services received during the SC program. 10% of pts were extremely dissatisfied or dissatisfied with how the results were explained after the procedure. Importantly, 64% of participants said they would not have completed the SC without the assistance of the PN.

Conclusions: PN, in an OAE program among low-income URMs, helps pts overcome barriers to SC. Nearly two-thirds of pts would not have undergone a SC without PN assistance. Overall, pts were highly satisfied with the SC program. APN program may help reduce racial disparities in CRC screening.

Depression following Acute Coronary Syndrome Is Not Associated with the GRACE 6-Month Mortality Index. D. Schwartz. Mount Sinai School of Medicine, New York, NY.

Background: Depression has been shown to be associated with increased mortality following hospitalization for acute coronary syndromes (ACS). While some researchers have argued that this association is a result of a biobehavioral mechanism linking depression with post-ACS mortality, others have argued that analyses linking depression with mortality failed to properly control statistically for cardiac disease severity. The measures thus far utilized to account for cardiac status have been varied and have not been validated to predict post-ACS mortality. We sought to assess whether cardiac severity could be a confounder of the relationship between depression and post-ACS depression by testing whether there was an association between depressive symptoms and the Global Registry of Acute Coronary Events (GRACE) score, a validated prediction model used to predict 6-month mortality after ACS.

Methods: A total of 457 post-ACS patients were enrolled within 7 days of their coronary event at 2 university hospitals. 413 (90%) completed follow-up at 3 months. The Beck Depression Inventory (BDI) was used to assess depressive symptoms at hospitalization. A BDI score ≥10 indicates symptoms of at least mild depression, while a score of 0-4 indicates minimal to no depression. The Depression Interview with Structured Hamilton (DISH) was used as an additional measure of depression at hospitalization. At 3 month follow-up, BDI and DISH assessments were repeated. Patients were characterized as either stable non-depressed, stable depressed, or as a remitter. Only 15 patients became newly depressed and were not included in further statistical analyses. Using clinical data obtained at the time of admission and through chart review, we calculated the GRACE risk-adjustment index to determine the patients' predicted six-month all-cause mortality from the time of hospital discharge. A GRACE score of 80 predicts a 1% mortality at six months, 100 predicts a 2% mortality, and >210 predicts a >50% mortality. We utilized ANOVA to compare GRACE index scores according to depression status.

Results: The mean age was 61 years (range 25 – 93), 41% were female, 11% were Hispanic, and 13% were Black. Patients with BDI ≥10 at admission had an average GRACE score of 92 (range 25 – 196), compared to 92 (range 32 – 187) for those with a BDI 0 – 4 ($p=0.90$). Similarly, patients who met DISH criteria for depression had no statistically significant difference in GRACE scores versus those who did not; 88 vs. 93 ($p=0.15$), respectively. At 3 months, the patients' depression status continued to show no statistical association with mean GRACE scores from admission. Using BDI classifications, averages were: stable non-depressed 91, stable depressed 86, remitter 91 (p=0.28). Using DISH classifications: stable non-depressed 92, stable depressed 87, remitter 89 (p=0.49).

Conclusions: Depressive status after hospitalization for ACS was not significantly associated with the GRACE score, a well-validated measure of cardiac risk severity. If higher mortality is found in the depressed patient group, our finding would strengthen the assertion that depression is an independent risk factor for mortality and that biobehavioral mechanisms such as poor adherence or neurohormonal mediators are causal links.

Impaired Beneficial Effects of Deep Inspiration in Obesity. M. Nudelman[1], S. Liautaud[1], A. Togias[2], H. Shaikh[1], A. Chiarelli[1], C. Schechter[3] and G. Skloot[1]. [1]Mount Sinai School of Medicine, New York, NY; [2]Johns Hopkins University, Baltimore, MD and [3]Albert Einstein College of Medicine, New York, NY.

Rationale: Airway responsiveness (AR) may be increased in obesity. Low tidal volumes in the obese (O) could increase AR by inhibiting the beneficial effects of deep inspiration (DI). We hypothesized that if this were true, O and nonobese (N) subjects should respond differently to routine (R - with DIs) but not to modified (M - no DIs) methacholine (Mch) challenge.

Methods: R and M challenges were performed in 8 O (BMI≥30) and 8 N (BMI≤25) nonasthmatics. Lung function included forced oscillation (FO) and spirometry at baseline and post-Mch (maximal efforts only) as well as after each dose step (for spirometry, maximal or partial efforts in R and M Mch challenges respectively). FO measured resistance at 5 Hz (R5) (global airways index), 20 Hz (R20) (large airways index), and 2 indices of small airways function, R5-R20 and the integrated area of low frequency reactance (AX) (all in cm H_2O/L/sec). Post-Mch % change from baseline was calculated.

Results (Mean±SE): Baseline lung function revealed significant differences in O vs. N subjects only in FEV_1/FVC (0.80±0.008 vs. 0.86±0.011, p=0.002) and in R5 (3.74±0.16 vs. 2.92±0.21, p=0.008). The mean highest dose of Mch given did not differ between the groups in either challenge. As expected, greater changes were induced by M vs. R challenge in both groups (based on spirometry). The % increase from baseline in small airways indices in the R challenge was greater in O subjects (R5–R20: 43±14 vs. 5±7, p=0.02; AX: 634±199 vs. 88±25, p=0.02) but no significant differences were found in the M protocol (R5-R20: 46±7 vs. 47±13, p=0.9; AX: 836±190 vs. 910±232, p=0.8).

Conclusions: Our results suggest that increased AR in obesity is due to impaired beneficial effects of DI and may be predominantly a small airways phenomenon.

Prognosis of Macrovascular Invasive Hepatocellular Cancer. T. Shao. Mount Sinai School of Medicine, New York, NY.

Background: Therapeutic options are limited for hepatocellular cancer (HCC) patients whose tumors invade major blood vessels. Surgical or locoregional therapies are often not feasible. Survival, infrequently reported has been < 4 months (m) in most series. We sought to better define outcomes and prognostic variables in unresectable macrovascular invasive (MVI) HCC.

Methods: We performed a retrospective analysis of patients evaluated at a medical oncology practice at a liver center during a 5-year period. Records of patients with HCC and tumor invading portal veins (main or branches), hepatic veins or inferior vena cava (IVC) were evaluated with respect to prognostic variables, therapy and overall survival (OS). We included patients who had MVI HCC at diagnosis or at recurrence following initial therapy. Patients with MVI HCC who underwent hepatic resection were not included in this analysis and will be reported elsewhere.

Results: Sixty-one MVI HCC patients were identified who met criteria. Ten had recurrence following prior resection, RFA or embolization; 51 (84%) had MVI HCC at diagnosis. Median age was 62 (range 27–82); 89% were male. Etiology was as follows: HCV 48%; HBV 16%; HCV/HBV 3%; alcohol 16%; PSC 2%; idiopathic 13%. Median OS was 3.2 m; 6-month OS was 23% and 1-year OS was 6%. Univariate analysis indicated that Child-Pugh class, ECOG PS and Barcelona and CLIP scores were strongly associated with OS. Tumor size and type of vascular invasion (branch vs. main vs. IVC) were not associated with differences in OS. A trend towards improved OS was noted in patients age > 60 (4.1 vs. 2.4 m; p = 0.14) and in patients receiving hepatic artery-based therapy (embolization or chemotherapy) (4.5 vs. 3.1 m; p = 0.06); patients receiving therapy had similar Child and CLIP scores, but better PS than those not receiving treatment.

Conclusions: MVI HCC is associated with grave prognosis and several of the major classification systems further accurately define prognosis. Additional multivariate analysis will help define the contribution of hepatic artery-based therapy.

Revising the ACR Criteria for Systemic Lupus Erythematosus. V. Singh. Mount Sinai School of Medicine, New York, NY.

Purpose: The Systemic Lupus International Collaborating Clinics (SLICC) has undertaken an effort to revise and update the current ACR classification criteria for systemic lupus erythematosus (SLE).

Methods: Seventy patients were recruited. They were categorized based on the diagnosis given to them at the enrollment site: 56 SLE; 2 undifferentiated connective tissue disease (UCTD); 5 RA, 1 Primary APS; 3 Secondary APS; 4 vasculitis; and 2 dermatomyositis. Case report forms captured clinical and serological features. Serum and plasma were collected and stored for each patient. Patient summaries based on the data from the case report forms were sent to the members of SLICC. 13 SLICC members entered their own diagnosis for each summary, and were asked to do so without regard to the number of ACR criteria. The agreement between SLICC members in their diagnosis for each patient was then assessed.

Results: Considering all the primary ratings, 656 (67%) were SLE, 312 (32%) were non-SLE, and 12 (1%) were uncertain. The Table summarizes the degree of agreement between the raters, overall, and as a function of whether the case satisfied 4 or more ACR criteria for SLE. Perfect consensus was reached for 33 (47%) of the patients. This exceeds the degree of consensus expected by chance (p<0.0001). Of the 27 cases with disagreement, 18 (67%) were due to a disagreement regarding whether the case was SLE or UCTD. The raters varied in the frequency of diagnosis of UCTD from 2 (3%) to 17 (24%). Among those patients with 4+ ACR criteria, perfect consensus was achieved in 24/47 (51%). The Kappa for this degree of consensus is 41%. Among those diagnosed with SLE but with less than 4 ACR criteria, perfect consensus was achieved in 9/23 (39%). The Kappa for this degree of consensus is 38%. The difference in consensus rate between the two groups is not significant (p=0.35).

Conclusion: Surprisingly, among experts in SLE, agreement is only fair in diagnosing patients as SLE who have 4 ACR criteria. There is no difference if there are 4 or 3 ACR criteria. The overlap in diagnosis between SLE and UCTD is large. Although 4 ACR criteria are used to classify patients as having SLE for clinical research purposes, it is obvious that this is not the standard adhered to by SLE experts in the diagnosis of SLE. The eventual goal is to develop criteria that would be both reliable and valid in the diagnosis or classification of SLE.

Real-Time Evidence-Based Medicine: An RCT of a Searching Tutorial. R. Stark. Mount Sinai School of Medicine, New York, NY.

Statement of Problem or Question: To practice Evidence-Based Medicine (EBM) in real-time, physicians must quickly retrieve evidence to inform their management decisions. Internal Medicine (IM) residents receive little formal education in electronic database searching, and have identified poor searching skills as a barrier to their evidence-based practice.

Objectives of Program/Intervention: (1) To teach IM residents to ask focused clinical questions about the care of hospitalized patients; (2) to increase IM residents' efficiency in searching PubMed and filtered EBM resources; and (3) to improve IM residents' comfort in searching for primary evidence to guide real-time patient care.

Description of Program/Intervention: The EBM Searching Tutorial was integrated into the inpatient ward rotation for IM residents at Mount Sinai Hospital in New York City. All PGY2 and PGY3 (n=88) residents were randomized to either participate in the searching tutorial or to attend control conferences unrelated to EBM. Residents randomized to the searching tutorial (n=44) meet in groups of 3–6 for one hour weekly for 4–8 weeks during the academic year. Each session is supervised jointly by a librarian and 1–3 faculty members from the Division of General Internal Medicine. During the sessions, each resident generates a clinical question about an active patient on the service, focusing on issues of diagnosis, prognosis or treatment. Using 3 computers in the room, participants then search the literature to answer their questions. Faculty directly supervise all searches, guiding strategies for searching PubMed and emphasizing the use of ACP Journal Club and the Cochrane database when appropriate. In the last 5 minutes of the conference, participants orally present their search strategy and the evidence that resulted from their search. Evaluation of the searching tutorial is two-fold. All 88 residents will complete self-assessment surveys before and after participating in the searching or control conference. The survey was developed by the SGIM EBM Task Force and measures EBM searching skills and comfort. In addition, searching skills will be measured with an objective structured clinical evaluation (OSCE). Participants will be asked to search for primary evidence to answer a series of clinical questions. Their ability to quickly find quality evidence, appropriate use of filtered resources, and searching techniques will be measured. Investigators scoring the OSCEs will be blinded to group allocation.

Findings to Date: We have surveyed 78 (89%) IM residents prior to the intervention. When provided with a clinical scenario, 95% and 96% report they would utilize PubMed or UpToDate®, respectively, to answer their question. More residents would consult with a peer (64%) or a specialist (50%) than use filtered resources such as Cochrane (26%) or ACP Journal Club (28%). Despite reporting high use of PubMed, only 35% of respondents report feeling very comfortable using it. Few residents report being very comfortable using Cochrane (6.7%) or ACP Journal Club (2.7%). Post-intervention surveys and OSCE evaluations are ongoing.

Key Lessons Learned: IM residents frequently use online textbooks (UpToDate®) and PubMed to answer clinical questions, but rarely use filtered resources. Their self-reported comfort with PubMed and filtered resources is low. We hypothesize that real-time teaching of searching skills in the context of patient care will improve these skills and promote evidence-based practice.

Limitation of the Resting Ankle–Brachial Index in Symptomatic Patients with Peripheral Arterial Disease.

R. Stein, I. Hriljac, J.L. Halperin, S.M. Gustavson, V. Teodorescu, and J.W. Olin. Mount Sinai School of Medicine, New York, NY.

Abstract: Peripheral arterial disease (PAD) has been demonstrated to be prevalent in the primary care setting. However, it has also been shown to be unrecognized and under-treated. Owing to the association with cardiovascular disease it has been recommended to screen high-risk patients for PAD in the primary care setting using the ankle-brachial index (ABI). ABI has been demonstrated to be highly sensitive and specific in diagnosing PAD in patients with significant stenosis. However, the utility in patients with less severe stenosis and calcified vessels is in question. The aims of this study were to determine the diagnostic utility of measuring the ABI at rest in patients referred to the vascular laboratory for evaluation of suspected PAD, and to assess the added value of pulse volume recordings and post-exercise studies in patients with a normal ABI. A computerized vascular diagnostic laboratory database was queried for symptomatic outpatients referred for measurement of segmental blood pressure, the ABI or pulse volume recordings by physicians not specialized in the evaluation and management of patients with peripheral vascular disease. Of 707 patients undergoing outpatient physiologic arterial evaluations between February 1, 2003 and July 31, 2004, 396 met these inclusion criteria. Data recorded included resting ABI, ABI following treadmill exercise test and the presence of abnormal pulse volume recordings. The study population ($n = 396$) consisted of equal numbers of men and women (mean age 69 years, range 19–100 years). Among 396 studies, resting ABI values were normal in 183 (46.2%) and abnormal in 159 (40.2%). Of the 138 patients who underwent exercise testing, 84 had normal ABI readings at rest. In the 84 patients who had a normal ABI at rest and underwent exercise testing, the ABI fell below 0.9 after exercise in 26 (31%). Arterial non-compressibility was detected in 54 (13.6%) patients, whose average age was 67 years. Thirteen (24%) of those with non-compressible vessels had abnormal pulse volume recording (PVR) results, compared to five with normal resting ABI who had abnormal PVR findings (2.7%). In conclusion, this study demonstrated that nearly half of patients referred to the outpatient vascular laboratory because of suspected arterial disease had a normal resting ABI. While it is recommended that the ABI be measured at rest in patients at risk of PAD in primary care practice, these findings suggest that patients with symptoms of PAD should be more completely evaluated in a vascular laboratory. Furthermore, when the ABI is normal at rest in patients with symptoms of intermittent claudication, exercise testing is recommended to enhance the sensitivity for detection of PAD.

"Single-Bite" versus "Double-Bite" Biopsy Specimens: Is There a Difference?

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Background: Many gastroenterologists currently take endoscopic biopsies using the double-bite technique, in which two biopsy specimens are obtained during a single pass of the forceps. We hypothesized that the overall quality of biopsy specimens from the double-bite technique is inferior compared to specimens obtained from a single-bite technique.

Methods: The study was prospective and partially blinded. Endoscopic biopsies were taken using each technique. The double-bite technique involved taking an initial biopsy, repositioning the forceps, and taking another biopsy from the same area with the initial specimen still on the forceps. The single-bite technique involved removing the forceps with its specimen after a single bite. At each site, 4 specimens were obtained, 2 using the double-bite and 2 using the single-bite technique. The specimens were then sent to a single, blinded pathologist. The specimens were evaluated for: diameter (whether the sample was > 2 mm), depth (whether muscularis mucosa was present), percentage of specimens crushed, percentage of specimens torn or sheared, percentage of specimens that did not contain superficial epithelium, and overall diagnostic quality of the specimen (graded: 1=good, 2=moderate, 3=poor).

Results: Of the 29 patients enrolled in the study, 18 patients underwent EGD and 11 underwent colonoscopy. 74 biopsies were taken with each method. The pathologist received 71 of the 74 single-bite (96%) and 63 of the 74 (85%) double-bite specimens ($p=0.025$). 69 single-bite (97%) and 59 double-bite (94%) specimens had a diameter over 2 mm ($p=1.0$). 42 single-bite (59%) and 38 double-bite (60%) specimens had muscularis mucosa ($p=1.0$). 16 single-bite (23%) and 12 double-bite (19%) specimens were crushed ($p=1.0$). 50 single-bite (70%) and 42 double-bite (67%) specimens were torn ($p=0.1$). 35 single-bite (49%) and 33 double-bite (52%) specimens had no superficial epithelium ($p=1.0$). Of the single-bite specimens, 68 had an overall diagnostic quality grade of good, 2 had a grade of moderate, and 1 had a grade of poor. Of the double-bite specimens, 62 had a grade of good and 1 had a grade of moderate.

Conclusion: There is no difference in the overall diagnostic quality of biopsy specimens obtained from either the single-bite or double-bite technique. However, there are a statistically significant number of specimens lost from the double-bite technique when compared to the single-bite technique.

Discontinuation of Standing Opioid Orders for Individuals Transferred from Nursing Home to Hospital.

M. Suchanek, K.S. Boockvar, T.R. Fried, and R.S. Morrison. Mount Sinai School of Medicine, New York, NY.

Objectives: Patients in nursing homes commonly experience pain requiring continuous and potent analgesia; however, continuity of care for these patients is often interrupted by admission to the hospital. The objective of this study was to examine continuity of opioid prescribing when individuals are transferred from nursing home to hospital and to examine predictors and consequences of opioid discontinuation.

Methods: Participants were residents of six nursing homes (1 VA) admitted to three hospitals (1 VA) in the New York City metropolitan area between 1999–2004. Nursing home and hospital records were reviewed to identify medication regimens just before and after transfer between sites. Medications were matched and compared in dosage, route and frequency of administration. Associations between opioid use and patient demographics, physical function, comorbidity, APACHE illness severity, care setting (VA or non-VA), and hospital length of stay were examined in bivariate and multivariate analyses. A structured review of selected medical records was performed to ascertain the impact of opioid prescribing decisions between facilities.

Results: A total of 315 nursing home residents experienced 498 hospital admissions. On average patients were 81 years old; 57% were female, 52% white, 30% black, 12% Hispanic, and 50% demented. Patients were taking a routine opioid analgesic just prior to 72 (14%) hospital admissions. In 33 (46%) instances, routine opioid analgesia was discontinued upon hospital admission. After adjusting for demographic and clinical differences, patients in the VA setting were more likely to be taking an opioid analgesic prior to hospital admission (OR 2.58; 95%CI 1.04–6.44). No demographic or clinical characteristic was associated with opioid discontinuation. After controlling for illness severity and other clinical and demographic characteristics, opioid discontinuation was not associated with hospital length of stay. Additional results of structured review of selected medical records demonstrated incidences of patient withdrawl symptoms as well as sub-optimal pain control after interruption of opioid use.

Conclusions: Opioid discontinuation is common practice for individuals transferred from nursing home to hospital and is especially relevant in the VA setting. Further research is necessary to determine the appropriateness of opioid discontinuation and to investigate whether it is associated with patient outcomes such as pain, delirium, and withdrawal symptoms.

Impact: Improving continuity of opioid prescribing for patients transferred between sites of care could prevent iatrogenic harm.

Resections of Benign Hepatic Tumors. P.K. Sun[1], P. Martin[1], M.I. Fiel[2], S. Roayaie[2], P. Lopez[1], and M.D. Schwartz[2]. Departments of [1]Medicine, [2]Pathology, and [3]Surgery, Mount Sinai Medical Center, New York, NY.

Abstract: Benign hepatic tumors remain an important indication for hepatic resection. We review our experience of hepatic resections over a 15-year period at Mount Sinai Hospital, a major referral center for liver diseases located in New York City, to determine how the major indications for resection have changed and whether benign tumors are now a less frequent indication of hepatic resection. The service has performed over 250 resections of benign hepatic tumors since 1990. Through retrospective analysis of patient records, we examined: (1) the diagnoses of benign hepatic tumors resected at a major referral center, (2) the gender and age demographics of each diagnosis seen, and (3) how these factors have changed, if at all, over time. Between January 1990 and December 2004, 236 patients had surgical resection of benign hepatic tumors. The most common indications, in descending order, were hemangioma ($n = 90$; 38.1% of total subjects), simple cyst ($n = 42$; 17.8%), focal nodular hyperplasia (FNH) ($n = 36$; 15.3%), and hepatic adenoma ($n = 30$; 12.7%). For almost all diagnoses, the majority of patients were female (83.9% of all patients). Among common indications, FNH and simple cyst were associated with the highest percentage of female patients (FNH—94.4% females, 5.6% males; simple cyst—88.1% females, 11.9% males). Several less common diagnoses also had a marked female predominance: biliary cystadenoma, nodular regenerative hyperplasia, and angiomyolipoma were seen exclusively in female patients, and polycystic liver disease (92.3% females, 7.7% males) was seen almost exclusively in female patients. The mean age of all subjects was 48.1 years. Patients with FNH and hepatic adenoma had the youngest mean ages (36.5 and 38.2 years, respectively) among all diagnoses. The oldest mean ages were seen with inflammatory pseudotumor (62.0 years) and simple cyst (60.4 years). 39.2% percent of patients with laboratory data available had hepatobiliary abnormalities, most commonly mild elevations of alkaline phosphatase, transaminases, or total bilirubin. Benign hepatic resections comprised 22.8% of all hepatic resections over the 15-year study period. There were no clear temporal trends over the study period in the proportion of individual diagnoses, gender, or age, or the number of benign hepatic resections as a percentage of all hepatic resections.

Assessment of an HIV Educational Program in Ethiopia. M. Swaminathan and R. Hodes. Mount Sinai School of Medicine, New York, NY.

Background: HIV infection is a growing problem in Ethiopia. Educational programs have been implemented to reduce high-risk sexual practices and prevent the transmission of HIV but few studies have been conducted to test their effectiveness.

Methods: A total of 205 surveys were distributed amongst the clinic population of an NGO, which provides educational information as well as contraception. The survey assessed the attitudes and knowledge of HIV as well as towards safe sexual practices of the population. The population was also surveyed to determine their current sexual practices as well as their use of contraception.

Results: 58.4% of the population used some form of contraception in the previous year. Of these 12.4% used oral contraceptives, 50.5% used hormonal injections, and 1.0% used surgical sterilization. None used condoms or other forms of barrier contraception. 5.4% admitted to having sexual relations with more than one person in the previous year, 3.9% with someone they only knew casually and 1% admitted to having sexual intercourse with a commercial sex worker. There was much misinformation concerning HIV. Only 71.2% of patients believed condoms were effective in preventing acquisition of HIV, 29.9% believed that mosquitoes were carriers of HIV, 9.4% believed HIV was an airborne infection, and only 16.2% believed that abstinence was an effective protection against acquiring HIV.

Conclusion: High-risk sexual behavior is still prevalent as well as misinformation concerning HIV infection and transmission. Much work needs to be done in determining effective ways to change high-risk behavior beyond current educational and health promotion programs.

Palliative Care in the ICU. V. Veve. Mount Sinai School of Medicine, New York, NY.

Background: More than 60% of the approximately 2.5 million deaths in the US each year occur in hospitals. Almost half of these patients have been cared for in an ICU in the last 3 days prior to death. Hospital care for patients at the end of life is characterized by poorly controlled pain and other symptoms. Palliative care (PC) consultation for ICU patients has been growing; this is improving patient outcomes such as pain and symptom control, and family outcomes such as quality of care and satisfaction. Palliative care consultation in the ICU, can decrease hospital length of stay LOS and shift goals of care to comfort much earlier in the disease process for patients at high risk of death.

Objective: To describe pilot data on selected quality of ICU care indicators for patients who die in ICU. To examine differences in quality of ICU care for patients who received PC compared to usual care (UC).

Methods: Using the VA National Medical SAS Inpatient Datasets, we identified a cohort of veterans who died in the hospital at the VA between October 1, 2003 and December 31 2005 in ICUs with the length of last hospitalization greater than 48 hours. We developed a chart review tool to collect information on practice patterns in the ICU. The following information was collected: decision making by patient and/or family, evidence of advance directives, documentation of family meeting, evidence that the patient was considered dying, evidence of explicit plan of comfort care, presence of symptoms and symptom management, initiation of therapeutic interventions, discussion of their withdrawal, patient and family preference, whether PC was consulted or not, and death data. We will describe pilot data on selected quality of ICU care indicators for patients who die in ICU and examine differences in quality of ICU care for patients who received palliative care compared to usual care. We will determine the prevalence of selected quality of ICU care indicators for patients who die in ICU and examine with univariate descriptive statistics. We will use logistic regression to examine differences in prevalence of the four quality-of-care indicators for PC compared to UC patients. Control variables include patient age, diagnosis and reason for ICU admission and LOS.

Preliminary Results: Preliminary analysis shows that in FY04, a total of 132 patients died in the VAMC:84 (38.4%)in the ICU and 68 (31.1%)in the acute care wards. PC patients differed significantly from usual care patients in a number of ways. For example, compared with PC patients, UC patients had more comorbid conditions, were more likely to have a principal diagnosis of cardiovascular diseases but less like to have cancer, and were less likely to be on medical service. Multivariate results are forthcoming.

MMP-2 Regulates Collagen I mRNA Levels in Hepatic Stellate Cells: Potential Mechanism for Protective Role of MMP-2 in Liver Fibrosis. R. Vrabie, R. Gupta, J. Martignetti, M. Ramirez, F. Hong, B. Radbill, and M. B. Bansal. Mount Sinai School of Medicine, New York, NY.

Introduction: Matrix metalloproteinase-2 (MMP-2), a type IV collagenase produced by activated hepatic stellate cells, is increased in patients with chronic hepatitis and cirrhosis, suggesting a causative role in the fibrotic process. The current dogma suggests that MMP-2 is pathologic by accelerating the degradation of the normal basement membrane allowing for replacement by type I collagen, the collagen characteristic of the cirrhotic liver. Our lab has previously demonstrated that MMP-2 serves a protective role as MMP-2 -/- mice develop more histologic fibrosis (increased collagen I) in a toxin-induced model of liver injury and this increased fibrosis is not associated with differences in hepatocellular injury or degradation of collagen I but is associated with increased collagen I mRNA levels ($n=6$; 107% increase, $p<0.0001$). The mechanism by which MMP-2 regulates collagen I mRNA levels is not known.

Hypothesis: We hypothesize that MMP-2 directly regulates collagen I mRNA levels.

Methods: To determine whether endogenous MMP-2 is present within the nucleus of LX2 cells, a human hepatic stellate cell line, Western blot was performed on 30 µg of nuclear extract and probed for MMP-2. To determine whether MMP-2 is regulating collagen I mRNA levels, LX2 cells were transfected with either WT-MMP-2 or empty vector control. Effects of overexpression of MMP-2 on collagen I mRNA levels were examined by real-time PCR. In addition, to determine whether "MMP-2 knockdown" would have opposite effects on collagen I mRNA levels when compared to effects of MMP-2 overexpression, MMP-2 targeted siRNA (100 nm) or non-targeting siRNA (siControl) was transfected into LX2 cells and collagen I mRNA levels examined by real-time PCR. Transfection of non-targeting siRNA was used as a baseline to control for off-target effects of siRNA in these cells. To determine whether MMP-2 can transactivate the collagen I promoter, LX2 cells were cotransfected with WT-MMP2 or empty control vector along with collagen I promoter-Luciferase deletion constructs (2.2 kb, 1.8 kb, 906 bp, 220 bp, 133 bp, 120 bp, and 92 bp).

Conclusions: Both pro- and active MMP-2 were found within the nucleus of LX2 cells. Overexpression of WT-MMP-2 resulted in a 40% decrease ($n=5$, $p<0.014$) in collagen I mRNA levels and conversely there was a 66% increase ($n=4$, $p<0.001$) in collagen I mRNA levels in the LX2 cells in which MMP-2 had been "knocked down." These findings suggest a direct link between MMP-2 and collagen I mRNA regulation. Preliminary results of co-transfection of collagen I promoter-luciferase constructs and WT-MMP-2 suggests a potent repressor element located between 2.2 kb and 1.8 kb of the collagen I promoter. These results point to a novel role of MMP-2 in modulating gene transcription and will be explored in future studies.

Natural History of Dysplasia in Inflammatory Bowel Disease—Is Colonoscopic Surveillance of Dysplastic Lesions in IBD Justified? D. Wild, M. Sparrow, A. Cheifitz, P. Rubin, C. Bodian, and D. Present. Mount Sinai School of Medicine, New York, NY.

Background: There is no doubt that patients with long-standing inflammatory bowel disease (Crohn's Disease [CD], Ulcerative Colitis [UC] and Indeterminate Colitis [IC]) are at increased risk for colorectal cancer (CRC), several large reviews have estimated the incidence ratio to be 2–3 times that seen in the general population (1, 2). It is for this reason that a reason consensus panel advocates initiating a program of colonoscopic surveillance 8–10 years after the diagnosis of IBD is made and continuing every 1–2 years in attempt to achieve early detection of pre-malignant or dysplastic lesions (3). Once these dysplastic lesions are detected, there is a considerable amount of controversy surrounding how best to manage these patients. Studies have found the risk of low grade dysplasia (LGD) progressing to high grade dysplasia (HGD) or frank carcinoma ranges from 10–53% leading many specialists to advocate an aggressive approach that favors early surgical resection of colons in which any form of dysplasia has been detected (4, 5). An aggressive surgical approach is associated with a considerable amount of physical and psychological sequelae leading many patients and their practitioners to utilize a more conservative approach with frequent, careful colonoscopic surveillance, turning to surgery only after LGD is found on multiple serial exams or a lesion with HGD is detected. We performed a retrospective review of the charts of a single, experienced IBD specialist in an attempt to show that a careful conservative strategy could be utilized without significantly increasing the incidence or CRC or rates of death from it.

Methods: Utilizing colonoscopy result log books, we identified patients with IBD who at some point developed LGD, HGD or indeterminate dysplasia in either flat or polypoid mucosa as diagnosed by an experienced pathologist between roughly 1970 and 2005. We then retrospectively reviewed the patients' charts, recording all previous and subsequent colonoscopy and pathology results.

Results: While this study is still in the data analysis stage and so the final data is still pending, preliminarily we can say the following: we identified a cohort of 140 patients with IBD (87 with UC, 45 with CD and 8 with IC) who at some point had a dysplastic lesion. Eleven cases of CRC developed in the patients with UC, 5 cases of CRC were found in the patients with CD and 1 case was found in the patients with IC. The majority of cases of CRC were detected in an early stage that was entirely curable by resection.

Conclusion: No conclusions can be drawn until the data have been completely analyzed.

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Effect of Depression and Four Commonly Prescribed Anti-depressants on the Platelet Reactivity of Coronary Artery Disease Patients. M.U. Zafar, K. Hiensch, G. Vilahur, B. Ibanez, K. Davidson, J. Gorman, V. Fuster, and J. Badimon. Mount Sinai School of Medicine, New York, NY

Background: Depression is a frequently observed co-morbidity in coronary artery disease (CAD) patients following an acute coronary event. Conversely, depression in CAD patients has been linked to a higher incidence of recurrent coronary events. Although the mechanism of this relationship in not fully understood, it is presumably due to a higher serotonin-mediated platelet-reactivity in depressed CAD patients. There is some evidence suggesting that anti-depressive therapy can be helpful in reducing coronary events, but whether the mechanism is central or a direct effect on platelets remains unclear. We compared platelet reactivity in depressed vs. non-depressed CAD patients and assessed the effect of 4 commonly prescribed antidepressants on platelets.

Methods: Stable CAD patients with (n=13) and without (n=15) depression were enrolled. Depression was assessed using the Beck Depression Inventory using a cutoff score of ≥ 10. Patients on anti-depressive therapy were excluded. Platelet reactivity was assessed by optical aggregometry in response to adenosine disphosphate (ADP) (5μM) and serotonin (10μM). In order to assess the direct effect of the anti-depressive drugs (nefazodone, duloxetine, escitalopram and sertraline) on platelet reactivity, each drug was mixed *in vitro* with the patient's blood in separate tubes. Concentrations of the drugs were calculated to match plasma levels achieved with commonly prescribed clinical doses (nefazodone 200 mg/day, duloxetine 60 mg/day, escitalopram 10 mg/day and sertraline 100 mg/day). To serve as a comparative control, one tube of blood was mixed with equal volume of normal saline.

Results: Depressed CAD patients had higher platelet reactivity vs non-depressed CAD patients. Except for nefazodone, each drug significantly reduced serotonin-mediated platelet aggregation, with sertraline being the most potent. No effect on ADP mediated aggregation was seen.

Conclusions: Depressed CAD patients have increased platelet reactivity which plays an important role in the higher coronary event rate seen in this population. The effect on platelet reactivity exerted by the 4 anti-depressive drugs in our study was not the same. Sertraline appeared to have the most potent anti-platelet effect while nefazodone appeared to be the weakest. Our data strongly emphasizes the importance of selecting the proper anti-depressive therapy, particularly in CAD patients, if the dual benefit of improving depressive symptomatology and inhibiting platelet reactivity is to be obtained.

Antithrombotic Effects of Direct Factor-Xa Inhibition: A New Therapeutic Modality. M.U. Zafar, D. Vorchheimer, B. Choi, G. Vilahur, B. Ibanez, P. Moreno, V. Fuster, and J. Badimon. Mount Sinai School of Medicine, New York, NY.

Background: Cardiovascular disease remains the leading cause of death in the United States. Although potent therapeutic options are available, there is an ever-present need to discover newer, more novel methods to address this problem. Tissue factor pathway inhibition is a new therapeutic target in the treatment of atherothrombotic disease. Standard indirect factor Xa (FXa) inhibitors (i.e., heparin and warfarin) have proven to be effective but require cumbersome monitoring due to their bleeding complications. Injectable direct FXa inhibitors offer better safety, with efficacy comparable to current treatments. These benefits could be extended to the ambulatory setting with an oral agent. We evaluate the antithrombotic effects of an oral direct FXa inhibitor DU-176b in a phase I human study.

Methods: Healthy subjects (n=12, males=8, 28±6 years) received a single, 60mg dose of DU-176b. Antithrombotic effects of FXa inhibition were assessed by changes in thrombus size pre- and post-treatment, using the Badimon perfusion chamber. The chamber allows *ex vivo* perfusion of human blood over pig aorta at venous and moderately stenosed arterial flow conditions, resulting in thrombus formation over the pig aorta. Area of the thrombus is then measured using Image Pro Plus software. Chamber studies and measurements for anti-FXa activity and thrombin generation were performed pre-dose, and at 1.5-, 5- and 12-hours post-dose.

Results: Factor Xa inhibition by DU-176b resulted in a significant reduction in thrombus size and thrombin generation. The antithrombotic effect was rapid in onset, showing maximum effect after only 1.5 hours of dosing, and remained significant even at 5 hours. At 12 hours post-dose, the thrombus size was back to pre-treatment levels. Changes in thrombus size and thrombin generation closely followed the changes observed in the clotting parameters.

Conclusion: Factor Xa inhibition by DU-176b, a novel, oral, direct FXa inhibitor, significantly reduced thrombus formation (venous and arterial) and thrombin generation upto 5 hours post-dose. The antithrombotic effect mirrored changes in the clotting parameters, which could be used for monitoring in a clinical setting. The implications of Tissue factor pathway inhibition by DU-176b as a new therapeutic tool requires further study in larger clinical trials.

A Novel Nitric Oxide Donor (LA-419) Has Anti-thrombotic Properties in a Human Model of Thrombosis. M.U. Zafar, G. Vilahur, B. Choi, B. Ibanez, E. Salas, V. Fuster, and J. Badimon. Mount Sinai School of Medicine, New York, NY.

Background: Healthy endothlium exerts its protective antithrombotic effect via nitric oxide (NO) synthesis. NO is one of the most potent anti-platelet agents. Nitrates are known to have anti-platelet effect but only at supra-therapeutic doses. A NO donor exerting its effect primarily on platelets could offer the benefit of anti-platelet properties without prohibitive vasodilation. We studied the antithrombotic effect of a novel NO donor LA-419, with known anti-ischemic properties but no vasoactive effects.

Methods: Healthy males (n=8) received aspirin (325 mg/day) for 3 days prior to participating in 3 consecutive study arms; (a) LA-419 (10 mcg/mL) and (b) LA-419 (20 mcg/mL) and (c) abciximab (4 mcg/mL), serving as positive control. Non-anticoagulated blood was perfused through the Badimon chamber for anti-thrombotic assessments pre- and post-treatment, at venous and arterial flow rates.

Results: There was a dose-dependent decrease in thrombus formation at both venous and arterial flow conditions with LA-419. Abciximab was a very potent inhibitor of thrombus growth, as expected.

Conclusions: LA-419, a novel NO-donor, shows a dose-dependent antithrombotic effect, evidenced by a significant reduction in thrombus formation from baseline values, at both venous and arterial flow conditions. Our observations suggest that the availability of a NO-donor could prove beneficial in the prevention of thrombotic complications of cardiovascular disease and requires further clinical studies.

Left Atrial Size Can Identify the Highest Risk Multicenter Automatic Defibrillator Implantation Trial-II Patients for Ventricular Arrhythmic Events. A. Zohlman, L.B. Croft, D. Mehta, and M.E. Goldman. Mount Sinai School of Medicine, New York, NY.

Background: In the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II, implantable defibrillators (ICD) reduced mortality from 19.8% to 14.2% in patients with reduced left ventricular (LV) function and coronary artery disease over 20 months. However, in the control group, >80% of patients survived. Variables including QRS width, New York Heart Association class, LV ejection fraction (EF) or age were not predictive of survival. With 400,000 new eligible patients annually, the cost of ICD's would overwhelm the health care budget. Left atrial volume has been identified as a predictor of morbidity and mortality. Therefore we sought to evaluate whether left atrial area (LAA) or other echocardiographic (echo) parameters could identify the highest risk MADIT-II patients.

Methods: We retrospectively reviewed all patients over the last eight years that had an implantable cardiac defibrillator (ICD) placed from 1997 – 2005 and had an echocardiogram (echo) within a year of implantation. LAA, LV EF, 2-D LV size, wall stress, and ventricular events (episodes of ventricular fibrillation and/or ventricular tachycardia) requiring shock as documented by their ICDs were analyzed.

Results: Of 156 patients with ICD implanted and a recent echo, 60% met MADIT-II criteria. There was no difference in age, QRS width, LV EF, blood pressure or wall stress between patients with ventricular events and non-event patients. However, LAA (30 cm^2 vs. 25 cm^2, p=0.0004) was greater in those with at least one ventricular event.

Conclusion: LAA was a strong correlate of ventricular events which and potentially better identify the highest risk MADIT-II ICD eligible patients.

Jersey City Medical Center

Contrast Induced Neurotoxicity in a Patient with Normal Pressure Hydrocephalus. K. Patel, M. Ratanu, A. Andrade, and J. Matta. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Introduction: Contrast induced neurotoxicity is a rare but serious complication of coronary angiography. Non-ionic contrast media (CM) markedly decreases neurotoxic complications. Non-ion CM has been reported to cause transient cortical blindness, confusion and amnesia but no focal deficits, whereas ionic CM is associated with seizures, and motor and speech deficits. We report a patient who developed focal seizure and an acute confusional state after coronary angioplasty.

Case Report: A 65-year-old female with a history of DM presented for nausea and vomiting and ruled in for non-ST elevation myocardial infarction. She underwent transfemoral coronary angioplasty. Coronary angioplasty was done over 120 minutes, using 400 mL visipaque (iodixanol-non ionic CM). There wee no complications during the procedure. After 30 minutes, patient was found very confused with some twitching movement of tongue and right upper limb. CT head was done within 2 hours, which showed subarchnoid hemorrhage vs. meningitis. Within 36 – 40 hrs, the patient's mental status was improved significantly but she continued having nausea and dizziness. Repeat CT head next day still showed findings suggestive of subarachnoid hemorrhage. Third CT head showed contrast material stasis in the leptomeningeal vessels rather than subarchnoid hemorrhage. There was also evidence of communicating hydrocephalus. Retrospectively, patient's family claimed that patient had prior symptoms consistent with normal pressure hydrocephalus. Lumbar puncture was performed which showed protein 67 and normal opening pressure without any evidence of infection.

Discussion: We report on a patient who developed focal seizures and acute confusional state after coronary angioplasty. CM can cause neurotoxicity secondary to osmosis or embolism. We hypothesize that the symptoms here were due to direct toxic effect of contrast media, which in our patient stayed in contact with cerebral cortex for prolonged period of time secondary to the presence of normal pressure hydrocephalus.

Seizure Induced Neurogenic Pulmonary Edema. S. Hosadurga, K. Patel, M. Ratanu, A. Andrade, and J. Matta. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Introduction: Neurogenic pulmonary edema (NPE) characteristically presents within minutes to hours of a severe central nervous system insult. We report a patient who developed NPE after an episode of seizure.

Case Report: A 47-year-old African-American female with a history of hypertension and seizure disorder noncompliant to medication was admitted for witnessed tonic clonic seizures. Patient was found confused and short of breath after the seizure. Patient quickly desaturated to 88%. Physical examination revealed tachypnea, tachycardia and bibasilar rales that were consistent with pulmonary edema. Chest X-ray showed bilateral pulmonary edema. Stat CT scan showed diffuse infiltration consistence with pulmonary edema. Echo was normal. Patient's oxygen saturation improved with oxygen supplementation and seizures were controlled on Trileptal. Next day patient's mental functin and oxygen saturation improved. Repeat CT scan of chest within 24 hours failed to show any pulmonary edema. The diagnosis of NPE was made.

Discussion: The pathogenesis of NPE is not completely understood. Because the most common neurological events are associated with increased intracranial pressure, intracranial hypertension is considered a key factor. The results in stimulating the hypothalamus and vasomotor centers of medulla oblongata which leads to activation of the sympathoadrenal system and increased pulmonary capillary permeability. The outcome of patients with NPE depends on the initial neurological insult. NPE managed in a supportive and conservative fashion and usually resolves within 48 – 72 hours.

Clinical Suspicion Aids in Treatment of Toxic Ingestion Outcome. A. Kimel, C. Tadros, and D. Flores. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

A 54-year-old male was found by his family after stumbling, falling to the ground. He presented with confusion, blurry vision and elevated blood pressure. The patient had past history of severe depression. He denied any history of alcohol or any illegal drug use. ICU evaluation was called immediately as patient's mental status was deteriorating and became lethargic with respiratory rate of 8. He was intubated for airway protection and stabilization. On initial physical exam he was found to have slowly reactive pupils, not nystagmus, no oral-pharyngeal lesions, increased tone of the bilateral upper extremities and a decreased gag reflex. On breath exam there was a hint of a sweet odor. Patient was started empirically on antibiotics and aggressive hydration. Laboratory results revealed a sodium level of 138 (meq/l), potassium of 4.1, chloride of 111, bicarbonate of 9, BUN of 7, Cr of 112 and glucose of 112. Calcium was 9.0, magnesium was 2.2 and phosphorus of 2.7. An arterial blood gas analysis indicated severe metabolic acidosis. The anion gap was 1u with a calculated osmolar gap of 122. We began treatment for acute ethylene glycol poisoning based on high clinical suspicion. Fomepizole was administered at a dose of 15/mg/kg IV. Subsequently, the patient's creatinine increased 1.0 to 3.5mg/dL.

The patient became completely anuric within 30 hours of arrival. After failure of aggressive hydration, hemodialysis was instituted. Urine analysis revealed a urine oxalate level of 125 (units) and many calcium oxalate crystals. The family returned with an opened container of antifreeze found in the garage, but did not own an automobile. Our patient was extubated and did admit to a suicide attempt. The patient continued on hemodialysis for over one year due to severe renal impairment.

Discussion: Early in ethylene glycol intoxication the sole compound of ethylene glycol is present. As time passes, toxic metabolites accumulate and the patient develops metabolic acidosis. Eventually, oxalate is deposited in the kidney and elsewhere; renal insufficiency can occur. Once any of these manifestations occurs, antidotal therapy alone (used to block alcohol dehydrogenase with femoepizole or ethanol) is sufficient to treat the poisoning. In the presence of high clinical suspicion and laboratory data consistent with acute ethylene glycol ingestion, early administration of fomepizole is critical to avoid long-term sequella of renal failure in such intoxications.

IgA Nephropathy: Progression of Segmental Glomerulosclerosis and Crescent Formation after Complicated Pregnancy. T.S. Borisiak, K. Khan, E. Martinez and B. Weiner. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Case: A 32-year-old Pakistani female with no medical history of kidney disease or complaints, developed face and leg swelling and dark urine following 8 weeks s/p complicated pregnancy. In the second trimester she developed hypertension and in third became pre-eclamptic and was rushed into delivery via c-section at 36 weeks' gestation. As per medical records her renal function was within normal limits and urinalysis revealed slight proteinuria only in third trimester. She offered no complaints postpartum till present time. Labs on admission: Hgb, 11.3; Pl5, 454; BUN, 4; Alb, 1.1. LFT, within normal limits; hepatitis profile—negative; urinalysis 500 protein, >10 RBC, no casts; neg. serology for SLE and C3, C4 complement levels are within normal range. The 24-hour urine collection revealed massive proteinuria (15g/d). Renal sonogram was unremarkable. Renal biopsy was done. Pathology: IgA nephropathy, diffuse segmental endocapillary and sclerosis glomerulonephritis with crescent formation. Patient was discharged home on ACE inhibitors and furosemide for symptomatic relief.

Discussion: IgA nephropathy is a chronic progressive glomerular disease with infrequent reversal. Crescentic glomerulonephritis is a rare presentation of IgA nephropathy and associated with more rapidly progressive renal failure and poor prognosis. The increased renal blood flow and hyperfiltration that occur during pregnancy may potentially aggravate the sclerosing process.

Conclusion: Pregnancy could play an important role in worsening previously asymptomatic kidney disease.

Halitosis Heralding Pyogenic Liver Abscess. N. Javier, A. Obiefuna, C. Ukpong, and P. Bhatt. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Introduction: The liver is the most commonly involved organ in a visceral abscess. The two major mechanisms are local spread from continguous infections with the biliary tree or peritoneal activity, and hematogenous seeding. The latter is not the usual pathway.

Case: A 45-year-old male with hypertension, depression and mild mental retardation presented with a one-day history of right upper quadrant abdominal pain and fever. He had mild leukocytosis and hyperbilibubinema. Initial impression was of acute abdomen. Ultrasonography showed a hypoechoic hepatic mass. Computed tomography (CT) indicated acute cholecystitis vs. pancreatitis. The HIDA scan was normal. Chest X-ray was significant for right-sided inferior lung field infiltrate. A diagnosis of pneumonia with right-sided pleural base reaction was made. After starting IV antibiotics, the patient felt better despite having intermittent febrile episodes. He was advised completion of a 14-day regimen of oral antibiotic upon discharge. One, week later, the patient was readmitted for similar symptoms. However, the abdominal pain was more pronounced in the epigastrium. Another abdominal CT was done which revealed multiple lesions in the left hepatic lobe and porta hepatis. The patient underwent endoscopy that showed an extrinsic mass compressing the done subsequently. The specimen grew *Streptococcus viridans*. There was partial resolution of the hepatic lesions with dramatic improvement in the patient's symptoms. The amebic titer and tumor was unremarkable. On further history, the patient's mother had observed that her son had significant halitosis several months prior to the onset of symptoms despite daily oral hygiene. He was finally discharged on oral antibiotics and advised repeat CT with colonoscopy with one week.

Discussion: This case illustrates the variability and the non-specificity of the clinical presentation of patients with pyogenic liver abscess. Clinicians should therefore have a high index of suspicion. Hematogenous seeding from transient bacteremia either coming from the oral cavity or a possible underlying malignancy are proposed pathophysiologic mechanisms for the occurrence of a pyogenic liver abscess in an otherwise low risk patient.

The Enigmatic Kikuchi Fujimoto Disease. N. Javier, X. Mdluli, S. Kazmi, and R. Chinai. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Introduction: Kikuchi's disease is a benign, self-limiting clinicopathologic disease with protean and nonspecific symptoms. It occurs worldwide, affecting mostly Asian women.

Case: A 32-year-old male from South India presents with a 3 23k history of intermittent febrile episodes, chills, night sweats, fatigue and myalgia. He had no recent travel, vaccinations, exposure to pets and sick contacts, illicit drug use, sexual promiscuity, and occupational hazards. His initial work-up in the clinic included a negative Mantoux test and a normal chest X-ray. In the hospital, his physical exam was significant for multiple mobile anterior cervical right-sided lymph nodes. His blood tests showed leukopenia (2,000/mm^3), relative microcytosis, high LDH, and slight elevations in the ESR and AST. Differential diagnoses included viral and mycobacterial infections, lymphoma, connective tissue disease, immunodeficiency, and protozoal infection. Whole body tomography showed multiple lymph nodes in the cervical region. A second stage Mantoux test, malarial smear, and an HIV test were unrevealing. Serologic immune markers only showed a past exposure to CMV. A BMA with flow cytometry showed a marginally hypocellular marrow without evidence for leukemia or lymphoproliferative disorder. The modal excisional biopsy showed effacement of its architecture with necrotic areas surrounded by reactive and foamy histiocytes consistent with histiocytic necrotizing lymphadenitis or Kikuchi Fujimoto disease. Immunohistochemical studies were confirmatory with positive immunostains for CD 3, 20, and 68. The patient was being managed supportively with antipyretics, fluids and analgesics prior to discharge.

Discussion: The exact cause for Kikuchi Fujimoto disease is unknown. It is thought to be an exuberant T cell response to multiple nonspecific stimuli. The course subsides from a few weeks to 6 months. There is recurrence in 3% of cases. On complication is progression to SLE. The typical presentation includes lymphadenopathy, fever, night sweats, weight loss, fatigue, chills and polyarthritis. The disease could be confused with tuberculosis, malaria, lymphoma and lupus. An excisional biopsy with immunohistochemical testing is the gold standard. The medical management is mainly supportive.

Low Testosterone Levels in Males Evaluated for Autoimmune Disease. A. Kimel and R. Lahita. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Females predominate with autoimmune disease. Males who present with various autoimmune diseases like lupus, Sjogren syndrome and autoimmune muscle disease are often found to have low levels of androgens. Some of these males also have hyperprolactinemia. Patients with autoimmune disease and Klinefelter syndrome represent one group where levels of androgen are decreased. A total of 26 males were sampled from a large outpatient autoimmune disease practice. These males included 8 with SLE, 2 with RA, 7 with primary APLS, and 9 with other conditions. 42% of the males sampled were found to have hypoandrogenemia. Under no circumstances did the referring physician have any insight into the accompanying syndrome and none of the referring doctors noted gynecomastia or other feminizing physical signs. The average level of testosterone in the affected men was 135 ng/dL ± 5. The normal range of testosterone in the general population is 260 – 1,000 ng/dL. Only 4 men were found to have elevated levels of serum prolactin. The largest group of men with low levels of androgen was the men with the diagnosis of anti-phospholipid syndrome. The predominate class of autoantibody found in these men were the APLS antibodies. These data strongly suggest that low levels of androgen predispose men to autoimmune disease and are important to measure on initial presentation.

The Adherence to HAART in HIV (+) Pregnant Women: Retrospective Study in Hudson County. H. Park, O.Odeyemi, D. Kim, J. Shah, M. Lekkala, A. Obiefuna, A. Tochuku, E. Scarinci, and A. Grigriou. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Introduction: It is known that adherence to highly active antiretroviral treatment (HAART) in HIV (+) women is generally higher during pregnancy period than after delivery. However, there is not enough studies to support this and the causative factors for declining adherence were not well identified. This is a retrospective study for HIV (+) pregnant women in hudson county to identify the change of adherence to treatment during and after pregnancy and to identify the causative factors.

Methods: Among the HIV (+) pregnant women who are seen at the Family Health Center, the charts of 25 women who gave birth between

2002 and 2005 were analyzed retrospectively. The demographics, duration of disease, parity, mode of transmission, family structure, history os substance abuse, trend of CD4 and viral load, type of HAART regimen and adherence before, during and after pregnancy were analyzed.

Results: During the pregnancy 19 out of 25 (76%) showed good adherence. However, after delivery, only 12 (48%) were still maintaining good adherence. The good and poor adherence groups were compared. There were no significant differences in race, age, parity and previous history of substance abuse in the two groups. Those diagnoses with HIV during pregnancy were more adherent to treatment than those diagnosed before pregnancy. The number of active substance abusers and number of homeless were higher in the poor adherence group. The identifiable major causative factors in declining adherence included active drug use, lack of awareness of the consequence, denial, mental illness, poor family support structure and other co-morbidities.

Conclusion: This study showed that there is significant decline in adherence to HAART in HIV (+) pregnant women after delivery. The poor adherence group could be a high-risk group who could potentially spread HIV in the community. Special intervention should be implemented to improve the adherence especially after delivery.

Appropriateness of Digoxin Use in Elderly Patients. H. Chughtai[1], C. Buzuski[2], N. Reyes[2] and M. Reisner[1], Departments of [1]Medicine and [2]Nursing, Jersey City Medical Center, Jersey City, NJ.

Introduction: Previous studies have shown that digoxin may be overprescribed for elderly patients. We chose to study the appropriateness of digoxin use in elderly patients in Hudson County.

Methods: Cross-sectional study with patient survey and data analysis using descriptive statistics (frequencies). This preliminary data is based on 7 patients with a mean age of 81.7 years.

Results: 49.5% patients were taking digoxin for more that 5 years. Only 28.6% of the patients knew why they were on digoxin. 85.7% of patients were not aware of complications/side effects of digoxin. Of all the patients, only 71.4% had symptomatic heart failure. 28.6% patients had an exercise tolerance of more than 5 blocks, 14.3% patients had an exercise tolerance of less than one block and 57.1% of patient had an exercise tolerance of less than one block. 57.1% of patients were found to be concomitant ACE inhibitors, 14.3% on diuretics while using of B-Blockers was 42.9% in patients on digoxin. Regular cardiac rhythm was found in 71.4% of patient while irregular cardiac rhythm was found in 28.6% of patients. New York Heart Association functional class: 82.6 (class 1); 14.3% (class 2), 42.9% (class 3), 14.3% (class 4). Only 14.3% of all patients complained about symptoms suggestive of digoxin toxicity.

Conclusion: Our initial data confirms that many patients are on treatment with digoxin without being on maximal treatment with other first line drugs (diuretics, ACE inhibitors, B-blockers) making them susceptible to toxic side effects of digoxin. We plan to confirm our preliminary findings using data from 20 – 30 patients and also include echocardiographic parameters t confirm if patient truly need digoxin or not.

Queens Hospital Center

A Case of Pulmonary Cavitary Nodules in a Patient with Rheumatoid Arthritis Treated with Tumor Necrosis Factor Alpha Inhibitors. Jagruti Patel, Karen Mrejen-Shakin, Adriana Abrudescu, Department of Medicine, Mount Sinai School of Medicine, Queens Hospital Center, Jamaica, NY.

Introduction: Rheumatoid arthritis is characterized by inflammatory synovitis involving symmetrical peripheral joints. Although the course of this multisystem disease may vary many patients progress to polyarticular destruction of cartilage with bone erosions.

Macrophages and cytokines contribute to synovial inflammation and bone erosions. Drugs targeted at inhibiting the effects of the cytokine TNF-alpha have been developed: a soluble p-TNF-alpha receptor-IgG1 fusion protein, etanercept; and monoclonal IgG1 antibody against TNF-alpha, the chimeric infliximab; and the recombinant fully human adalimumab.

We report a case of a female with seropositive rheumatoid arthritis who developed pulmonary nodules when started on TNF-inhibitors.

Case Report: A 71-year-old female with a history of seropositive erosive rheumatoid arthritis (RA) who had failed various therapies, including methotrexate; was started on Etarceptl 25 mg twice weekly in 2002. PPD and a chest radiograph were normal. The following month the patient improved, having less joint pain, morning stiffness, and requiring less than 5 mg/day of prednisone. Approximately 8 months later, while on entanercept, the patient's rheumatoid arthritis flared and the decision was made to switch to adalimumab. The patient had improvement in the pain, stiffness and swelling of the hands, knees and ankle joints. After five months on adalimumab, the patient complained of cough, and fever. A chest radiograph revealed new cavitary pulmonary nodules. Repeat PPD was negative. CT scan of the chest showed diffuse thin walled cavitary nodules of different sizes. In November 2003, she had both a non-diagnostic fiberoptic bronchoscopy biopsy and CT-guided fine needle aspirate of the nodules. Cultures and acid-fast bacilli were negative. Adalimumab was discontinued and due to polyarticular pain, the patient was restarted on high dose steroids. At this point the patient had no pulmonary complaints and refused surgical biopsy of the nodules. Of note, since her rheumatoid factor, which was persistently positive prior to etanercept therapy, remained negative during both etanercept and adalimumab therapy, this excluded the possibility of rheumatoid nodules.

Repeat CT of the chest three months later showed that the nodules were getting smaller in size. In July 2004, because of relapsing polyarthritis, the patient was rechallenged with etanercept. Although the patient had no pulmonary complaints, a follow up CT of the chest in October 2004 revealed changes in the pulmonary nodules. Etanercept was discontinued. On January 10, 2005 a video-assisted thoracoscopic wedge resection of the left upper lobe and the lingula showed benign cavitary and non-cavitary necrotic lesions with inflammation. Acid fast bacilli cultures were negative. Since broth culture grew staphylococcus aureus and tissue culture grew pseudomonas aeruginosa, workup for an infectious source was done. Transesophageal echo, blood cultures, and gallium scan were negative. Emperic antibiotics were started with no improvement in the nodules. Subsequently, the patient was treated with Prednisone, average daily dose between 10 – 20mg/day. Follow-up CT scan showed slight decrease in the size of the lung nodules.

Discussion: The cause of rheumatoid arthritis is unknown. Patients have hyperplastic synovial membranes, with increased vascularity and inflammatory cells, primarily CD4+T-cells. Anti-TNF-alpha drugs such as etanercept, infliximab, and adalimumab have been developed. These drugs have rare, although significant, side effects: reactivation of mycobacterium tuberculosis complex disease, mycobacterium avium-intracellulare complex disease, and a non-specific lung injury characterized by non-caseating granulomas.

Since our case demonstrated a temporal cause-and–effect relationship between the development of the pulmonary cavitary nodules and the treatment with TNF-alpha inhibitor medications, we suggest that these biologic drugs may also induce an inflammatory nodular-cavitary lung reaction.

Chronic Unexplained Diarrhea with Macroscopically Normal or Nonspecific Colonoscopy Results. What Next? Kanwardeep Arora[1], Narayan Agrawal[1], Fred Rosner[2] and Svetlana Grinblat[2] [1]Department of Medicine, Queens Hospital Center, Jamaica, NY, and [2]Department of Pathology, Elmhurst Hospital Center; Mount Sinai School of Medicine, New York, NY.

Introduction: Chronic diarrhea and abdominal pain is a common problem in the elderly and occasionally is difficult to diagnose etiologically. We discuss a patient who presented with chronic watery diarrhea and crampy abdominal pain, whose initial work-up was negative. The patient's biopsy showed collagenous colitis (C/C) initially thought of and treated as *Clostridium difficile* colitis.

Case Report: An 82-year-old obese Hispanic woman with hypertension, atrial fibrillation, and seizure disorder presented with chief complaint of diarrhea for 2 weeks. The patient was recently discharged from another hospital where she was treated with IV antibiotics. Diarrhea started three days after discharge and was characterized by multiple watery bowel movements/day associated with intermittent abdominal pain. Medications included Dilantin, zocor, digoxin, moxifloxacin and coumadin. Physical examination was non-contributory. Routine laboratory tests were normal CT of the abdomen was non-specific. The patient was with flagyl, ceftriaxone, loperamide and prevacid. Colonoscopy was non-specific. *C. difficile* assay was negative. The patient improved symptomatically and was discharged but was readmitted after 2 weeks with similar watery diarrhea for 5 days. Biopsy taken during the previous colonoscopy was positive for collagenous colitis (CC) patient was started on mesalamine and cholestyramine. Patient was started on and zocor and prevacid were stopped because of their possible association with C/C was concurrently treated for C.difficile. Diarrhea resolved and the patient was discharged only on mesalamine. Currently the patient is asymptomatic.

Discussion: Microscopic volitis (MC), comprising of CC and lymphocytic colitis (LC) are uncommon entities. Characterized by chronic, watery, secretory diarrhea with a normal or near normal gross appearance of the colon on colonoscopy. It occurs most-commonly in the sixth decade of life. The rate of 9 – 10 % in different studies in patients with chronic watery diarrhea indicates the necessity to consider the diagnosis of MC in older individuals with diarrhea and normal colonoscopy. Biopsy is diagnostic, with CC the major microscopic characteristic is a thickened collagen layer 7–100 μm (normal: 1–7 μm) and with LC, an increase in the number of intraepithelial lymphocytes (IEL) often above 20 per 100 epithelial cells; (normal IEL: 3–5 per 100 epithelial cells). The pathogenesis of MC is unclear. Synchronous collagenous and pseudomembranous colitis have also been described, suggesting a possible etiologic role for *C. difficile*. MC has been linked to **simvastatin**, **lansoprazole**, NSAIDS, flutamide, ranatadine, gold salts and **ticlopidine**. The mechanism of the diarrhea is decreased absorption of sodium chloride accompanied by active chloride secretion.

Treatment is based mainly on anecdotal studies. Possible offending drugs should be stopped and the antidiarrheal of choice is loperamide. Various therapies that have been bismuth include budesonide, sulphasalazine, cholestyramine and bismuth. A trial of bismuth, sulphasalazine or cholestyramine usually should be attempted before treating the patient with steroid therapy.

Conclusion: Microscopic colitis should be considered in an elderly person with chronic persistent watery diarrhea with normal or near normal colonoscopy. Multiple biopsies should be routinely taken for histopathology in such cases including biopsies of the right side of the colon thus increasing the diagnostic yield. The possibility of medication-induced MC should always be considered and the possible offending drug should be stopped and the effects observed.

Effect of Albumin Polymorphism on Thyroid Hormones. Michael Aninyei, Vijayatha Gundarapu, David Reich, Paul Kim, Fred Rosner, and Issac Sachmechi. Department of Medicine, Mount Sinai School of Medicine, Queens Hospital Center, Jamaica, NY

Introduction: Thyroid hormones (T3, T4/TH) circulate in the blood bound to carrier proteins: thyroxine-binding protein (TBG), transthyretin (TTR), prealbumin and human serum albumin (HSA).

While 99.97% of T4 is bound in the following distribution: TBG-75%, TTR-15%, only 10% is HSA bound with 0.03% existing as free T4 (FT4). T3, on the other hand is 99.7% bound, though less avidly, with 0.3% free.

Because free thyroid hormones exist in equilibrium with its carrier proteins, any factor that affects the quantity/ quality of the carrier, invariably affects the pharmacokinetics and pharmacodynamics of TH. This is best exemplified in familial dysalbuminemic hyperthyroxinemia (FDH), an autosomal-dominant disorder characterized by increased total T4 (TT4), elevated FT4, normal TSH and T3 level, as measured by one or two step immunoassay. Some rare cases of increased T3 have been described. We describe a case of a patient with FDH presenting with symptoms of hyperthyroidism.

Case Report: A 79-year-old Hispanic man with a history of hypertension, schizoaffective disorder, benign prostatic hypertrophy and chronic renal insufficiency was admitted for evaluation of wide complex tachycardia found on his outpatient 24 hr holter monitor done to evaluate his complaint of frequent palpitations.

The patient acknowledged that he had had palpitations for several years and that he is always nervous. He also stated that this "nervousness runs in the family." There was no associated weight loss, unusual hair loss or visual changes. He also denied any neck mass/goiter, diarrhea or abnormal skin rash/thickening but stated that his hand always "shakes." He denied any chest pain or shortness of breath, either at rest or with exertion. He also denied any orthopnea or paroxysmal nocturnal dyspnea but complained of chronic leg swelling with no recent change. Exercise tolerance remained very good and unchanged.

On admission, endocrinology consult was called for evaluation of persistently increased TT4 and FT4 levels. Vital signs were stable and physical examination revealed only a mildly anxious elderly man with coarse tremors of the hands on extension. The rest of the examination was unremarkable. Sonogram of the thyroid gland showed bilateral prominent lobes, left greater than right. Thyroid I-123 uptake scan was 19.4% (NL 15-40%).It also showed a mildly enlarged but non-palpable lower pole of the left thyroid lobe with homogenous activity throughout the gland. Thyroid function tests (TFTs) were done using routine automated direct one step/two-step immunoassays. These showed normal TSH levels of 1.22 and 0.78 (NL 0.34–5.6 mu/mL); T3 levels were normal at 98.4 and 125.3 ng/dL (NL 87–178). However, TT4 and FT4 levels were increased: FT4 levels were 2.25 and 2.34 ng/dL (NL 0.58–1.64), TT4 levels were 17.58 and 18.69 (NL 6.09–12.2). Free T3 by equilibrium dialysis was 402 ng/dL (normal 230–420) and alpha subunit for pituitary hormone was less than 0.3ng/mL (NL<1.0). Free T4 by equilibrium dialysis was normal-2.1 ng/dL (NL 0.8–2.7)

Cardiac work up including echocardiogram, cardiac enzymes, stress test and telemetry monitoring was unremarkable. He was treated with a beta-blocker and discharged after being assured that his thyroid condition was benign.

Discussion: The above case report and thyroid function tests results fit the classic description of FDH, an autosomal-dominant disorder characterized by increased TT4, increased FT4 (as measured by one/two step immunoassay but normal by equilibrium dialysis), normal or rarely increased T3 and normal TSH. It is common among Caucasians, especially of Portuguese and Hispanic (Puerto Rican) descent with a reported incidence of about 1.8%. It was first described independently by henneman et al and Lee et al in 1979, and it wasn't until 1994 that Petersen and Sunthornthepvarakul, independently of each other, identified the precise genetic defect.

The central problem is the presence in the serum of a naturally occurring mutated albumin. This missense mutation in the HSA gene results in the replacement of the codon 218, which is normally arginine, with histidine following a guanosine→adenosine transition in codon 218 in one of the two alleles. The effect of this mutation is an albumin with 10–15-fold greater affinity for T4 and a 5 fold greater affinity for T3.

Other mutations involving the same codon 218 and codon 66 have been described. Important in the differential diagnosis is a TSHoma—a rare condition characterized by increased or normal serum TSH and elevated thyroid hormone levels with a high alpha subunit. The patient is usually thyrotoxic and MRI usually shows a pituitary tumor/hyperplasia. Thyroid hormone resistance syndrome is another important differential, characterized clinically by goiter and elevated/normal serum levels of TSH and elevated TH. It is rare and inherited in an autosomal-dominant fashion. The primary defect in the majority of the cases is one or more mutations in the TH receptor beta.

Conclusion: Familial dysalbuminemic hyperthyroxinemia is usually benign and does not usually require treatment unless there is a concurrent different thyroid dysfunction. Because of the paucity of knowledge of this condition, particularly among non-endocrinologists, there is a tendency for inappropriate treatment including RAI, medications and thyroid surgery. Hence, the need for extensive education on this condition. **NL=normal level.

Empiric Management of Acute Dilated Cardiomyopathy Two Years in Retrospect. Keside Amaechi, Subrahmanya Siripurapu, Rakhil Rubinova, and Sharad Jaitly. Department of Medicine, Queens Hospital Center, Mount Sinai School of Medicine, Jamaica, NY.

Introduction: Dilated cardiomyopathy refers to disease of the myocardium with associated chamber dilatation and cardiac dysfunction. It may be sequel to a variety of insults to the heart or it may be idiopathic. Irrespective of etiology, the acute management of dilated cardiomyopathy is strictly clinically based.

We report a case of acute dilated cardiomyopathy, pericarditis and myocarditis in an 18-year-old male, which was successfully managed using only empiric therapy and still found to be clinically stable two years later.

Case Report: The patient is an 18-year-old black male Rugby player from England who presented at the emergency department with complaints of chest pain, palpitations and dyspnea. He denied fever, but had a 'flu' infection about 4 months previously which resolved spontaneously. He had no coronary artery disease risk factors. He had a normal lung exam, 1st and 2nd heart sounds, but with added rub. Electrocardiogram showed widespread ST segment elevation, and troponin I was elevated. He was admitted to the coronary care unit for acute pericarditis. Echocardiogram showed ejection fraction of 25%, global hypokinesis, 4 chamber dilatation and in-chamber spontaneous echo contrast. Concomitant myocarditis was immediately suggested and patient was started on empiric treatment consisting of initial heparin, warfarin (with target INR 2.0), beta blockers, asprin, angiotensin converting-enzyme inhibitors (ACEI) and digitalis, while subsequent echocardiograms and troponin I levels began to show improvement. Antibodies to mycoplasma, cytomegalovirus, cocksakie and echo viruses were negative as was the anti-nuclear antibody testing. A left heart angiogram and endomyocardial biopsy confirmed myocarditis, showing myocardial inflammatory cells with cellular necrosis on microscopy; and normal coronaries. Ten days later, his ejection fraction rose from 25–50% and he was discharged on low-dose ACEI and warfarin.

Discussion: The prevalence of dilated cardiomyopathy is estimated to be 36 / 100,000, and 80% are usually classified as idiopathic. At least 20% of patients have familial forms of the disease with mutations in genes encoding cytoskeletal or nuclear membrane proteins. This disease is genetically heterogenous in transmission and there is no evidence for routine formal testing. Most patients pursue an inexorably downhill course, and will die of heart failure or arrhythmia within 3 years of diagnosis. Spontaneous improvement occurs only with 25% of patients. Antiarrythmics are best avoided because of their proarrythmic potential, instead consider insertion of cardioverter-defibrillator in patients with symptomatic ventricular arrythmias. Endomyocardial biopsy is usually not necessary, but it is helpful in the recognition of secondary cardiomyopathies such as amyloidosis. In patients with advanced disease that are refractory to medical therapy, cardiac transplantation should be considered. Timely assessment and symptom-directed inpatient therapy is critical in improving outcome and mortality.

Conclusion: Dilated cardiomyopathy is the cause of approximately 25% of all causes of congestive heart failures and the primary indication for cardiac transplantation in the US. Retrospective studies over the past 20 years by Matsumara et al have shown a trend towards decreasing mortality with the increasing use of angiotensin-converting enzyme inhibitors, beta blockers, and the avoidance of antiarrythmics. However, the value of simple supportive, and empiric therapy at the time of initial diagnosis is emphasized and could be the most important single factor in early stabilization of what is still largely an unknown disease.

Fibrillary Glomerulonephritis. Garima Gupta, Fred Rosner, and Stafford John. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: Fibrillary glomerulonephritis (FGN) is a rarely diagnosed ultrasturctural, immune-mediated entity characterized by infiltration of mesangium and glomerular basement membrane by fibrillary deposits that are negative on congo-red and thioflavin-T staining but are reactive for polyclonal IgG and C3.

Case Report: A 22-year-old woman was admitted to our hospital for progressively increasing leg swelling. Her physical examination showed uncontrolled hypertension and bilateral lower extremity pitting edema. Her laboratory values included: Blood urea of 5 mg/dL, serum creatinine of 0.6 mg/dL, total cholesterol of 448 mg/dL and LDL of 342 mg/dL, albumin 1.5 g/dL. Urinalysis revealed proteinuria of >300 mg/dL, with microscopic hematuria. At this time, work up for glomerulonephritis was started, 24-hour urinary protein excretion was 3.8 gms. Tests for autoimmune antibodies, which included anti double-stranded DNA antibody titer, anti-nuclear antibody titer, anti sm-RNP, anti -Sm antibody, anti-Ro, anti-La antibody were all negative. Laboratory workup failed to show a paraproteinemia, cryoglobulinemia or acute or chronic infection with hepatitis B and C. Renal ultrasound showed increased paranchymal echogenicity of both kidneys with thickening of the cortex.

A renal biopsy was performed to evaluate the cause of the very significant proteinuria. Light microscopic examination showed diffuse increase in the mesangial matrix and hyline material, which was periodic acid-schiff (PAS) positive and negative for thioflavin-T and congo-red stains. Only a rare lobule had a mild increase in mesangial cellularity. Many tubular loops showed membranous-like changes and extensive spicules and double contouring on the epithelial side. The renal tubules had a high profusion of hyaline droplets in the proximal tubular segments. The renal arteries and arterioles did not show any significant changes. Electron microscopy of the glomeruli revealed numerous non-branching fibrils measuring 21 nm in cross section located in the mesangium and many capillary walls. Some areas of glomeruli basement membrane were unremarkable while most contained numerous broad areas of fibrils that separated the podocyte from glomerular basement membrane. There was extensive effacement of the podocyte foot processes. Above- mentioned PAS positive and Congo-red and thioflavin-T stain negative amyloid-like deposition in mesangium under light microscopy which showed were non-branching fibrils of 21 nm in cross sections are collectively diagnostic of fibrillary glomerulonephritis.

Patient was treated with simvastatin for hyperlipidemia. The patient continues to have proteinuria with the 24 hr protein excretion increasing to 5.1 gm with stable blood urea and creatinine.

Discussion: FGN is an idiopathic glomerular disease characterized by randomly arranged congo-red negative fibrils of 16–24 nm in diameter. FGN needs to be differentiated from a related entity called Immunotactoid glomerulopathy (ITG) with larger microtubular deposits, usually > 30 nm in diameter arranged in a mostly tactoid manner. This is important because FGN is associated with a low incidence of systemic diseases whereas ITG has been linked to a high incidence of lymphoproliferative diseases and monoclonal gammopathy. The incidence of FGN is less than 1% in a renal biopsy series. The clinical course of FGN in previously-reported cases has varied from almost asymptomatic disease to fulminant renal failure. Symtomatic patients can present with proteinuria, hematuria, hypertension and renal insufficiency that progress over months to years. This disease entity does not respond well to corticosteroids or cytotoxic drugs and end stage renal disease develops within 2–4 years in about half the patients. Fibril deposition recurs in more than 50% of allografts but with benign course. Further studies of glomerular fibrillogenesis are needed to develop more effective treatments for this condition.

The Effect of Folic Acid on Thyroid Hormone Replacement. Asad Chaudhary, Afshin Tavakoly, Fred Rosner, and Isaac Sachemechi. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: Folate is considered one of the nutrients that is essential for many biochemical reactions within the human body. Folate and its role in erythropoiesis have been emphasized. Likewise, folate deficiency and its after-effects have been, clearly associated with homocysteins loads. However, folate and its effect on preexisting hypothyroidism have not been discussed in the medical literature.

The patient under discussion is a 36-year-old Guyanese woman who was diagnosed with Hashimoto's thyroiditis and polycystic ovarian syndrome with positive anti-thyroid peroxidase antibody at the age of 27 years. She had been followed in the Endocrine Clinic since then. Her baseline health status was unremarkable, as she was an otherwise healthy middle age woman, with a height of 5'2", weight of 125 lbs with body mass index of 22, vital signs have always been within the normal range, BP= 110 125/6075 mmHg, PR=6878 bpm. serum TSH=1.732.28 mIU/mL in 2005.

Her outpatient medications included levothyroxine 100 mcg /day which was increased to 125 mcg/day for six days in a week, since a seven day regimen would cause palpitations. No EKG record of paroxysmal or consistent atrial tachycardia or atrial fibrillation was reported.

In May 2005, her TSH was found to be 1.76, which had trended down to this level with months of treatment with levothyroxine. Other laboratory findings were unremarkable. Since she decided to conceive a child, she was advised to take prenatal vitamins and folate and was discharged from the clinic with no further changes in her medications. On her subsequent visit, she was complaining of tiredness, muscle pain, cramps, slight weight gain. Physical examination showed only slow relaxation of deep tendon reflexes, which were otherwise symmetrical. However, her TSH level increased had from 1.76 to 11.76 mIu/mL. The patient said she was compliant with folate and prenatal vitamin pills and especially took her levothyroxine as prescribed. No reasonable explanation was apparent. However, folate was removed from her regimen other medications were continued as they were. On the next visit, the TSH decreased from 11.76 to 3.00 m IU/mL, symptomatically the patient felt better and physical examination was unremarkable.

Discussion: Concomitant administration of folic acid to a patient who was receiving levothyroxine for the treatment of hypothyroidism, with euthyroid status evidenced by normal TSH and FT4, resulted in deterioration of the thyroid status, symptomatically as well as by marked increase in TSH. This may be an incidental finding, yet a significant one. The mechanism may be multi factorial, either decreased absorption of levothyroxine from the gastrointestinal tract with concomitant administration of folic acid, or an increase in the clearance of levothyroxine. The answer is unknown. Prospective studies examining this issue are recommended.

Impact of the Diabetes Center Team on Metabolic Parameters of Newly Referred Patients. David Reich, Sumera Ahmed, Michael Aninyei, Paul Kim, Sangita Parab, Manjulatha Nukala, Giti Mansouri, Hildegarde Payne, Betti Meenattoor, Clarita Avaricio, Aliyamma Samuel, Fred Rosner, and Issac Sachmechi. Division of Endocrinology, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Background: Most studies have shown that the majority of diabetic patients do not achieve American Diabetes Association (ADA) guidelines for clinical care. Studies have also shown that improvement in glycemic, blood pressure, and lipid control can have a favorable outcome in terms of reduction of microvascular and macrovascular complications.

Queens Hospital Center (QHC), a municipal hospital in the City of New York, serves patients from varied ethnic groups that suffer a disproportionately high prevalence of diabetes and its complications. Many of the patients are uninsured, meaning they have to purchase diabetes-testing supplies out of pocket. Furthermore, many of the patients have low health literacy. These are all factors that can impede successful management of the diabetic patient.

Aims: To assess changes in metabolic parameters of newly referred diabetic patients not at ADA recommended care on one or more metabolic targets, after referral to the QHC Diabetes Center of Excellence.

Methods: This is a retrospective cohort study employing electronic medical record review of 425 newly referred diabetic patients to the QHC Diabetes Center from January 2004 to August 2005. These patients, upon initial visit to the diabetes center, were not at the ADA recommended level on at least one of the following ADA clinical guidelines: A1c, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum triglyceride (TG) level, serum LDL cholesterol level or absence of nephropathy screening within the year preceding initial visit.

These patients were followed for a minimum of 3 months and a maximum of 1 year in the Diabetes Center. The mean changes in the above-mentioned ADA metabolic parameters were calculated if the initial parameter failed to meet ADA recommended goals.

Statistical calculations, including paired t-tests to determine the p-value, were performed using the SAS software program.

Results: Of the 425 patients referred to the Diabetes Center, 374 (88%) had an A1c $\geq 7\%$ on initial presentation. Of these patients, the mean change in A1c was a reduction by 2.0% ($P<0.0001$). For patients that had an initial A1c $\geq 9\%$, the mean change in A1c was a reduction by 2.8% ($P< 0.001$). Of the 425 patients referred to the Diabetes Center, 246 (58%) had an initial LDL cholesterol level $\geq$ 100 mg/dL. Of these patients, the mean change in LDL was a reduction by 40 mg/dL ($P<0.0001$). Of these 246 patients, 116 had an initial LDL $\geq$ 130 mg/dL, and the mean LDL decreased by 55 mg/dl in these patients ($P<0.0001$). Of the initial 425 patients, 149 (35%) had an initial TG level $\geq$ 150 mg/dL. The mean change in these patients was a decrease in serum TG level of 105 mg/dL ($P<0.0001$). Of the initial 425 patients, 263 (62%) were not at the recommended goal systolic blood pressure (they had SBP$\geq$ 130 mmHg), and the mean change in systolic blood pressure of these patients after referral to the Diabetes Center was a decrease of 18 mmHg ($P<0.0001$). Of the initial 425 patients, 153 (36%) were not at the recommended goal for diastolic blood pressure (they had DBP$\geq$ 80 mmHg), and the mean change in diastolic blood pressure of these patients was a decrease of 11 mmHg ($P<0.0001$). Of the 425 initial patients, data on baseline urine microalbumin testing was obtained on 392 and 263 (67%) had a urine microalbumin screen within 1 year prior to referral to the Diabetes Center. Of the 33% that did not have screening for microalbumin on presentation to the Diabetes Center, 107 (82 %) had a urine microalbumin screen done when they were referred to the Diabetes Center.

Discussion: Diabetic patients had statistically significant beneficial changes on many metabolic parameters after referral to the QHC Diabetes Center. Although many of the patients were probably still not at the actual ADA recommended goal for some, or, in some cases, all of these parameters, the changes seen would be expected to have a favorable long-term impact on diabetes-related complications. For example, a reduction in A1c of only 1% would be expected to reduce microvascular complications by at least 25% and macrovascular complications by about 15%. A reduction in LDL cholesterol of 30% would be expected to reduce macrovascular endpoints by at least 25%, and a 10 mmHg reduction in systolic blood pressure would reduce microvascular and macrovascular complications and the risk of death by 35%.

Conclusion: Diabetic patients referred to the Diabetes Center of Excellence had significant improvement of their metabolic parameters. The success of the findings of this study is the product of a team approach, involving physicians as well as diabetes educators and dieticians. Barriers that may prevent more diabetic patients from achieving favorable changes in metabolic parameters should be identified and addressed.

A Medical Dilemma: Intracerebral Hemorrhage in a Patient with Lupus Exacerbation. Can Herpes Simplex Virus Be a Cause of Intracerebral Bleeding? Asad J. Chaudhary, Garima Gupta, Fred Rosner, and Adriana Abrudescu. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: In this era of better understanding, more treatment options and higher diagnostic modalities, sometimes diseases are not that simple.

Case Report: A 19-year-old man with no significant past medical history presented with progressively increasing swelling of all 4 extremities for 3 – 4 days and sharp chest pain, which was severe, non-radiating but increased with deep inspiration. Physical examination was significant for a blood pressure (BP) of 160/100 mm/Hg, pulsatile precordium, and painful movement of small joints of both hands. Initial laboratory tests showed proteinuria and anemia with a hemoglobin of 7.3 mg /dL. Erythrocyte sedimentation rate was increased to 145, rheumatoid factor was 87. Immunofluorescence assay for anti double stranded DNA antibody titer was elevated at 1: 160. Antinuclear antibody (ANA) titer was also elevated at the level of 1:2560 with a speckled pattern. Serum Complement 3 and Complement 4 were decreased to levels of 43 and less than 10, respectively. Considering the results of these tests, a diagnosis of systemic lupus erythematosus (SLE) was made. The patient was treated with antihypertensive therapy and 1000 mg of solu-medrol daily for 3 days. Renal biopsy was planned to assess the proteinuria. On the day of renal biopsy, the patient signed out against medical advice (AMA). One day later the patient presented with dizziness and headache and was found out to have a BP of 160/100 mm/Hg. He was not taking his antihypertensive medications. His blood pressure was brought under control with medications overnight but he again signed out AMA the very next day. One day later he again presented with "the worst headache of my life" and fever with right sided upper lip blister. His BP at that time ranged between 140 – 160/90. 100 mmHg, he had no neurological deficits but mild neck rigidity. CT scan of the head showed right temporal hemorrhage with surrounding vasogenic edema. Dexamethasone (6mg IV q6hours) was given after an initial bolus for cerebral edema. Serum for anti HSV1 and 2 antibodies were positive for IgG against HSV type 1 (HSV1). Acyclovir was given empirically. Lumber puncture (LP) was discussed as an option to reach a definite diagnosis but was postponed due to cerebral edema. EEG was normal and MRI failed to show any mass lesion in the brain or any evidence of vasculitides, treatment with intravenous Acyclovir was given. Lumber puncture was done after repeat CT showed a decrease in the cerebral edema. The cerebro-spinal fluid was positive for antiHSV1 IgG and HSV by PCR was undetected. Acyclovir was continued for a total of 10 days as well as oral prednisone 60 mg daily.

Discussion: Systemic lupus erythematosus is a chronic, occasionally life-threatening, multi-system disorder. Herpes simplex virus type 1 causes fulminant necrotizing meningo-encephalitis distinguished from other encephalitides by its focal and often hemorrhagic nature. Specific anti viral therapy with acyclovir can significantly improve the prognosis.

Summary and Conclusion: Our patient is a young male who presented with active multisystem SLE and while receiving high-dose maintenance corticosteroid therapy developed right temporal brain hemorrhage which may have been due to herpes simplex infection. Despite the inconclusive herpes simplex laboratory investigations, the decision to treat herpes simplex infection was made and resulted in a significant clinical improvement. Our patient walked out of the hospital on his own feet and with a smile on his face.

Marijuana Abuse a Nexus between Spontaneous Pneumomediastinum and a Sleeping Beauty. Michael Aninyei, Praveen Ponnamreddy, Habibur Rahman, Ricardo A. López. Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: The association between pneumothorax, pneumomediastinum, subcutaneous emphysema and drug abuse is well described in the literature. Various mechanisms including Muller's maneuver and Valsalva maneuver during drug abuse have associated. We report the delayed onset of pneumomediastinum and subcutaneous emphysema after marijuana use in a sleeping 20-year-old male.

Case Report: JL presented to the Emergency Department with sudden onset of chest pain, tightness and shortness of breath that awoke him from sleep one hour prior to presentation. He also complained of worsening chest tightness with deep breathing and cough that was productive of yellow sputum but no fever or chills. He had similar episodes as a child that resolved spontaneously. He smoked marijuana about two hours prior to developing the symptoms, during which he had inhaled deeply against a "closed throat."

On examination he was anxious, tachycardic and tachypneic. Pulse oximetry was 92% on room air. There was no tracheal deviation but there was mild intercostal recession. Auscultation revealed diminished bilateral breath sounds with diffuse rhonchi and wheezing. Subcutaneous crepitus was present in the suprasternal notch, neck and upper chest. The rest of the exam was unremarkable.

CXR and CT chest revealed diffuse pneumomediastinum with subcutaneous emphysema. The patient was admitted to ICU and treated with supplemental oxygen and bronchodilators. Daily CXR's revealed progressive improvement and he was discharged with appointments for outpatient follow-up.

Discussion: Pneumomediastinum is classified as primary spontaneous (non-traumatic) and secondary (traumatic). The non-traumatic type is very common in young adults. It occurs in any condition that creates a gradient between intra-alveolar and surrounding interstitial pressure with resultant alveolar rupture. Two mechanisms include: over inflation and increased alveolar pressure, which commonly occurs in expiratory airflow obstruction and glottic closure as in intentional Valsalva maneuvers (e.g., inhalational drug abuse), asthma, prolonged violent coughing, parturition, etc.

Alveolar rupture resulting from a sudden reduction in interstitial pressure caused by extreme inspiratory effort and reduction atmospheric pressure as in rapid mountain climbing, sudden return to surface from diving or air travel.

Secondary traumatic pneumomediastinum is often associated with prior trauma with perforations of the air and or food passages. Examples include intubation, endoscopy, esophageal rupture, etc.

Alveolar rupture leads to interstitial emphysema where fine air bubbles track along the bronchovascular bundle, coalescing into larger air collections in the mediastinum that can spread along the fascial planes causing pneumomediastinum, pneumothorax, subcutaneous emphysema, pneumoretroperitonium and even pneumoperitonium.

Clinical manifestations include chest pain, cough, dyspnea, mediastinal crunch and subcutaneous crepitus. CXR usually shows lucency surrounding the heart mediastinum and bronchovascular bundles.

The majority of simple non-traumatic pneumomediastinum resolves spontaneously; however in some cases pleural and/or mediastinal decompression may be required. Secondary traumatic cases are treated as necessitated by etiology.

Conclusion: The link between marijuana and PPM appears to be the Valsalva maneuver commonly employed during its use. Unexplained PPM should prompt a search for inhalational drug abuse. Symptoms may be delayed by hours as seen in our patient.

Massive Embolic Stroke following ERCP in a Patient with Atrial Fibrillation. Kalavagunta Satish, Nimesh Shah, and Farshid Radparvar. Department of Medicine, Mount Sinai Service at Queens Hospital Center, Jamaica, NY.

Introduction: Acute ischemic stroke is a well-known complication of atrial fibrillation (AF). Acute massive embolic stroke leading to brain herniation as a consequence of paroxysmal AF has rarely been reported.

Case Report: An 80-year-old woman was admitted to the surgical service with a complaint of abdominal pain suggestive of acute pancreatitis. Further work up comprising CBC, amylase level and abdominal ultrasound established a diagnosis of gall stone pancreatitis. An ERCP was recommended for which she underwent a cardiac evaluation for procedural clearance. EKG, echocardiogram and stress test were performed which revealed that she had paroxysmal atrial fibrillation. Patient developed a focal neurological deficit after ERCP. CT scan revealed a massive CVA involving the right side of the brain eventually leading to subfalcian herniation and death.

Discussion: In our patient the etiology of the stroke was thought to be of cardioembolic origin. One of the determinants of this outcome in atrial fibrillation is its duration. Several clinical trials have shown a reduction in the risk of stroke upon anticoagulation in paroxysmal AF. There has been no study comparing the severity of the neurological insults between the various types of AF.

Conclusion: We present a case of a massive CVA in a patient with paroxysmal atrial fibrillation. Our suggestion is that, irrespective of the duration of the paroxysms of AF an aggressive peri-procedural anticoagulant approach has the best outcome.

Polymositis as Initial Presentation of Breast Cancer in a Patient with Primary Sjögren's Disease. Michael Aninyei, Ebima Okundaye, Fred Rosner, and Adriana Abrudescu. Department of Medicine, Mount Sinai School of Medicine, Queens Hospital Center, Jamaica, NY.

Introduction: Polymyositis (PM) is an inflammatory myopathy associated with an increased incidence of cancer, though to a lesser degree than dermatomyositis. This increased incidence is further heightened by the presence of an additional connective tissue disease. We report a case of breast cancer presenting initially with polymyositis in a woman with Sjögren's disease.

Case Report: A 55-year-old woman with a history of primary Sjögren's disease, hypertension, diabetes mellitus, and a family history of a sister with breast cancer presented for a routine follow up in our rheumatology clinic, complaining of progressive proximal muscle weakness and pain of two months duration that was associated with frequent falls. She also complained of dry mouth, difficulty swallowing food and required "lots of water to push it down." There was no history of fever, odynophagia, cough or rash. There was no joint pain or swelling, no night sweats but the patient had defined weight loss.

Physical examination revealed decreased power/motor strength in both proximal lower extremities. She had a dry oral mucosa. There were no skin rashes and no joint inflammations. Reflexes, sensation, cerebellar functions were normal as were the cardiac, chest, breast and abdominal examinations.

Laboratory results showed elevated levels of creatine kinase-846 and aldolase-20. Serum anti nuclear antibody (ANA) was strongly positive as were the Ro and La antibodies, rheumatoid factor 152 and C reactive protein-10 were increased. Anti-Jo 1 antibodies were negative. Serum thyroid stimulating hormone (TSH), electrolytes and magnesium levels were also normal.

Chest roentgenogram and esophagram were normal. Non-contrast CT scan of the head, chest, abdomen and pelvis revealed pretracheal, precardiac and multiple enlarged bilateral axillary lymph nodes. Mammogram showed a new 1 cm ill-defined nodular density and a cluster of micro-calcifications in the inner lower quadrant of the right breast that later proved to be low grade ductal infiltrating carcinoma on biopsy with negative sentinel node sampling.

Quadriceps muscle biopsy showed increased fiber size variation with focally increased endomysial fibrous connective tissue and lymphoplasmacytic infiltrate. It also revealed numerous strongly esterase-positive inflammatory cells in the endomysial connective tissue. There was an abundance of T-cell and histocytes but no B cells. The patient responded to treatment with steroids with resolution of her active polymyositis. She also underwent a right mastectomy and is currently receiving hormonal therapy.

Discussion: The temporal relationship between myositis and malignancy is well known. However, the etiology of this relationship is still mainly hypothetical. Compared to the general population, the incidence of cancer among patients with dermatomyositis (DM) and polymyositis (PM) was 15% and 9% respectively, in a to Swedish study. This incidence was much higher-27% in patients with myositis and an additional connective tissue disease, as reported in a recent Australian study but still lower than that of DM-42%. Our patient belongs to this category in that she already had Sjögren's disease. Our case also remains a rarity among the published literature. The malignancy can occur prior to, at or after the onset of myositis, though the peak incidence is within 2 years prior to or after onset of myositis.commonly associated malignancies include ovarian, bladder, gastrointestinal, cervical, pancreatic, non-Hodgkin lymphoma and nasopharyngeal cancers. Mammogram and pelvic exam should be performed in female patients with PM.

Conclusion: We present a patient with PM. Knowledge of the association of PM with cancer prompted an active search for malignancy that revealed the presence of breast cancer which was appropriately treated.

There is a need to actively search for malignancy in patients with PM or DM. This is the proper standard of care according to the American College of Rheumatology. The use of only routine screening tests may be inadequate to find the cancer.

Recurrent Chest Pain in a Young Woman. Diana Arévalo, Habibur Rahman, Ricardo López. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Case Report: DC is a 33-year-old woman who presented with complaints of right-sided pleuritic chest pain and shortness of breath starting two days prior to her menses. She denied any other symptoms. Her medical history was significant for hemoptysis and a spontaneous right pneumothorax in her home country, Jamaica, W.I. in 2003 that subsequently was complicated by a hydropneumothorax. The pleural fluid was exudative and negative for infection and malignancy. She was treated initially with chest tube drainage but her lung failed to re-expand, and she developed a hemorrhagic hydropneumothorax prompting a fiber optic bronchoscopy and video assisted thoracoscopy. The bronchial tree was normal and washings were non-diagnostic. Thoracoscopy revealed hemorrhagic fluid and a collapsed right lung encased in a peel. Pleural biopsies revealed nonspecific inflammation. The right hemidiaphragm had fenestrations and hemorrhagic tissue over it, biopsies of which revealed endometrial glands and stroma. These findings were consistent with endometriosis. The patient's hospital course was complicated by an empyema, which was treated with antibiotics, decortication and pleurodesis. She was then started on Depo-Provera 150 mg via intramuscular injection monthly for six months. After six months of treatment, the patient developed a pulmonary embolus following a long car ride. She was treated with anticoagulant therapy for six months and the hormonal therapy was discontinued. The patient remained asymptomatic until presenting with her current presentation.

Her physical examination during her recent admission was significant for reduced breath sounds on the right with dullness to percussion. Her CBC revealed mild microcytic anemia and her serum chemistry was normal. A spiral CT was negative for emboli, but demonstrated a loculated right pneumothorax without air-fluid levels, ipsilateral mediastinal shift and a loculated pleural effusion consistent with a trapped lung. Lower extremity Doppler ultrasound did not identify any thrombus. The patient's symptoms resolved with analgesics. The patient was discharged home, with continued follow up in the Chest clinic. PFTs three months after discharge revealed an insignificant tendency toward restrictive changes with preserved gas exchange. The patient continues to have recurrent chest pain preceding her menstrual cycle that responds to analgesics.

Discussion: Thoracic endometriosis is a rare occurrence with 110 cases reported over 28 years. Of these, the most common presentation was pneumothorax in 73%, followed by hemothorax in 14%, hemoptysis in 7 %, and lung nodules in 6%. Chest pain is the most common symptom and is present in 90% followed by dyspnea in 33%. Histopathologic demonstration of thoracic endometrial tissue is not always necessary, diagnosis is usually clinical and therefore requires a high index of suspicion. Treatment is usually hormonal suppression of ovulation, if it is unsuccessful or if the patient cannot tolerate hormonal therapy then pleurodesis is usually successful. Despite therapy, most patients continue to experience catemenial chest pain as in our patient.

Conclusion: Thoracic endometriosis is a rare entity among woman of childbearing age; its diagnosis requires a high index of suspicion. Recurrent chest pain is common despite appropriate therapy; physician awareness of this fact will preclude unnecessary and potentially harmful diagnostic testing.

Refeeding Syndrome—Underdiagnosed and Undertreated. Chinar Mehta, Heather McKenzie, Valeriy M. Vilensky, and Ricardo A. López. Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Case Report: LE is a 68-year-old man who presented with recurrent falls, generalized weakness, and poor oral intake of 4–6 weeks duration. Recurrent falls he attributed to being weak; his knees gave up on attempts to ambulate. He had lost 60 lbs in the last 3 months. Past medical history includes depression and peripheral vascular disease. Physical examination revealed an emaciated elderly man. A 6 × 5 cm ulcerated, foul smelling skin lesion with surrounding erythema was noted on his left temple, later diagnosed as a sebaceous carcinoma. He had dry gangrene of the toes of his right foot and absent pedal pulses. WBC was 19K with 4% bandemia. Serum prealbumin was 1.2 mg/dL (normal = 16–30 mg/dL), albumin was 1.2 g/dL (normal = 3.5–5.2 g/dL), and remaining blood chemistries were undermarkable. CXR and head CT were unremarkable. An evaluation for metastatic spread of the skin cancer was negative.

Intravenous antibiotics were administered for cellulitis surrounding the skin lesion. Surgical consultants were called for possible tumor resection and foot amputation.

Dietary consult for malnutrition was obtained and a caloric count revealed that the patient was only consuming 50% of his goal calories, despite oral supplements and feeding assistance from the nursing staff. Enteral nutrition via nasogastric tube was initiated with a prescription containing 1,809 cal/day (34 cal/kg IBW), 109 g of protein (1.6 g/kg IBW), (28 NP cal/kg IBW) and 1,392 cc of total volume.

The next day patient was found to be in acute respiratory distress. Serum chemistries revealed hypernatremia, hypokalemia, hypomagnesemia, and hyperglycemia. CXR showed congestive changes. The patient was transferred to the MICU, where he was treated with antibiotics, an insulin infusion, electrolyte supplementation, and intravenous hydration. He clinically improved after the tube feeds were held and the electrolytes corrected, but later he developed progressive mental status changes requiring intubation for airway protection. He continued to deteriorate and expired after cardiopulmonary arrest.

Discussion: Refeeding syndrome (RFS) is a metabolic complication that occurs in patients who have undergone a period of starvation and are started on aggressive enteral or parenteral nutrition. RFS occurs in up to 0.8% of hospitalized patients and can be as high as 30–38% with TPN.

In RFS, the body shifts from protein and fat catabolism to carbohydrate metabolism. Glucose becomes the primary fuel source. This stimulates an increase in insulin production which leads to increased cellular uptake of glucose, phosphate, magnesium, and potassium leading to decreased serum concentration of these ions. These metabolic derangements can lead to cardiac, respiratory, and neuromuscular dysfunction, and even sudden death.

It is therefore recommended that the daily caloric intake in severely malnourished patients initially not exceed 15 cal/kg, with no more than 100 g of carbohydrates and 1.5 g/kg of protein. Electrolytes should be replaced liberally. Fluid intake should be limited to 800 cc/day plus maintenance for insensible losses. Caloric intake can then be gradually increased after the first week with a goal weight gain of 1.5 kg/wk or 0.25 kg/day.

Conclusion: RFS is an underdiagnosed and undertreated condition which can be potentially fatal if not recognized, when severely malnourished patients are fed aggressively. Joint efforts by medical, nursing, and dietary staff can prevent this fatal but preventable condition.

Retained Peritoneal Glossypibioma Mimicking Angina Pectoris. Ebima Okundaye, Micheal Aninyei, Julio Vaquerano, Leelavathi Kasturi, Fred Rosner, and Henry Safier Henry. Department of Medicine, Mount Sinai Services at Queens Hospital Center, NY.

Introduction: Intra-abdominal foreign bodies, following open surgical procedures have been reported on numerous occasions. One of the foreign bodies inadvertently left in open abdominal surgeries is the gauze sponge. The gauze sponge, a cotton derivative, serves primarily as a blood-mopping device in surgical procedures. Retained gauze sponge (glossybipoma) can cause symptoms related to its mechanical presence.

Case Report: We present a 56-year-old man, with a history of hypertension, non-compliant with his medications, and a history of cholecystectomy 10 years prior. He presented with exertional chest pain radiating to the left arm and epigastrium. The patient underwent a cardiac workup including serial EKGs, cardiac enzymes and stress test, which showed normal myocardial perfusion. The patient was discharged but was readmitted with recurrent symptoms. An esophagogastroduodenoscopy was performed and *H. pylori* negative gastritis was found.

CT scan of the abdomen revealed a mass lesion on the lesser curvature of the stomach extending to the left lobe of the liver. A subsequent exploratory laparatomy showed an encapsulated fibrinous mass adjacent to the stomach, which was excised along with a portion of the adjacent gastric wall. Histology revealed a 10×5×4 cm gauze sponge with secondary granulomatous changes and evidence of focal and purulent material secondary to involvement of the gastric wall.

Discussion and Conclusion: Retained gauze sponge following surgery may produce a clinically symptomatic radiologically apparent mass lesion. This diagnosis should be considered in the differential diagnosis of chest pain radiating to the epigastrium in a patient with a history of abdominal surgery. To our knowledge, this is one of the few cases of a glossybipoma gauze sponge causing symptoms after a long period of clinical dormancy and is unique because of its presentation as substernal chest pain radiating to the left arm and epigastrium.

Streptococcus gordonii Septic Arthritis and Endocarditis in a Patient with Rheumatoid Arthritis Receiving Etanercept Therapy. Alexander Mbewe, Adriana Abrudescu, Seong K. Choi, Fred Rosner, and Lambert King. Department of Medicine, Mount Sinai School of Medicine, Queens Hospital Center, Jamaica, NY.

Introduction: Septic arthritis is a medical emergency which, if not promptly treated can lead to significant morbidity and mortality. Prompt recognition and treatment are critical to ensure a good prognosis. Several risk factors predispose selected patients to septic arthritis such as age greater than 60 years, diabetes mellitus, a remote focus of infection, intravenous drug use, immunosupression, presence of inflammatory arthritis, joint trauma and/or the presence of a prosthesis. We describe an elderly patient with long-standing rheumatoid arthritis (RA) who developed streptococcus septic arthritis and endocarditis while on treatment with etanercept for RA.

Case Report: A 61-year-old woman with a long standing history of seropositive RA presented with three days of increased pain and swelling of the left knee.

Medical history was significant for rheumatoid arthritis for the last 14 years, rheumatic heart disease, hypertension, prior cerebrovascular accident, asthma and seizure disorder. She had no history of recent dental work. She has been treated with etanercept and hydroxychloroquine for the past three years and her RA was in remission.

On physical examination, she was febrile at 101° degrees centigrade, had tachycardia of 109/min, with normal blood pressure. There was no evidence of dental caries. There were no skin rashes or skin infarcts. There was a grade 2/6 systolic murmur over the mitral area. There was no hepatosplenomegaly, and no lymphadenopathy. The left knee was swollen, warm, tender with a large synovial effusion and severe functional impairment. Initial laboratory findings: white blood cells 9,700 with 82% neutrophils, and erythrocyte sedimentation rate of 128 routine serum chemistries and liver function tests where normal as was the urine analysis. Approximately 100 mL of purulent fluid was aspirated from the left knee. The joint fluid had a white blood cell count of 127,000 (92% polys, 3% lymphocytes, 5% monocytes) glucose 20 mg/dL, and protein 3.7mg/dL.

Blood cultures and synovial culture results were positive for *Streptococcus gordonii* (the streptococcus viridans class), sensitive to vancomycin, ceftriaxone, erythromycin, clidamycin, and chloramphenicol.

Transesophageal echocardiography was done which revealed a thickened mitral valve with severe mitral regurgitation and a thin mobile vegetation measuring 1.2 cm in length, consistent with endocarditis.

The patient was treated with vancomycin serum levels were in the therapeutic range. The patient developed new onset expressive aphasia and right-sided hemiplegia. A repeat head CT showed a hemorrhagic stroke and mitral valve surgery was deferred due to the risks associated with anticoagulant therapy. The patient was transferred to a rehabilitation unit with antibiotics being continued for a total of three months.

Discussion: Etanercept is a competitive inhibitor of tumor necrosis factor (TNF) at the cell surface receptor and regulates the biologic activity of TNF. There is concern regarding the vulnerability to infection in patients treated with TNF inhibitors.

Streptococcus viridans is a heterogenous group of streptocci which are normal flora found in the human nasopharynx and gastrointestinal tract and commonly found in dental caries and subacute bacterial endocarditis (SBE), especially in previously damaged valves such as in rheumatic heart disease. However, it is uncommon to find viridans streptococci in septic arthritis.

In our patient, it is likely that an already structurally compromised rheumatic mitral valve was the initial focus of infection, with seeding probably originating from the patient's oral flora. Subsequent systemic dissemination then led to left knee septic arthritis and cerebrovascular embolic phenomena. However, the rapidity of systemic spread over a period of five days, despite adequate antibiotic therapy, may have been due to an immunocompromised state secondary to prior etanercept therapy. To our knowledge this is a unique case report of *S. gordonii* septic arthritis in a rheumatoid arthritis patient treated with etanercept.

Intestianl Pseudo-obstruction as the Initial Presentation of Systemic Lupus Erythematosus in a Male Patient. Jonathan Marquez, Fred Rosner, and Adriana Abrudescu. Department of Medicine, Mount Sinai School of Medicine, Queens Hospital Center, Jamaica, NY.

Introduction: Systemic lupus erythematosus (SLE) is a disease with multi-system involvement which presents with a myriad of clinical manifestations, signs and symptoms. Although it is common for SLE to present with rash, ulcers, arthralgias, or systemic symptoms such as fever or fatigue. We present a rare case of intestinal pseudo-obstruction as an initial presentation of SLE.

Case Report: A 33-year-old African-American man with no significant past medical history presented with cramping left lower quadrant abdominal pain with anorexia, nausea and vomiting for two days. The patient had no melena, hematochezia, or hematemesis. There was no history of recent travel, no sick contacts, no recent intake of medications or new food items, and no history of surgery. The patient has a 5-pack-year smoking history, but denied illicit drug use or alcohol intake. On physical examination, the patient was ill-appearing, tachycardic and hypertensive but afebrile. He had no skin rashes, no oral ulcers, no palpable lymphadenopathy, and no joint swelling. His chest was clear, and his heart examination was normal. On abdominal exam, the patient had direct and rebound tenderness with guarding over the left lower quadrant, hypoactive bowel sounds. Rectal exam showed good sphincter tone, no tenderness, with guaiac-negative brown stool.

Pertinent laboratory tests including a complete blood count showed only mild thrombocytopenia. Routine serum chemistries were normal as were serum electrolyte levels and renal function, was liver function tests revealed mild elevations of AST and GGT and LDH, along with hypoalbuminemia of 1.9. Urinalysis showed protein of more than 300 mg/dL with occasional coarse granular casts. Serum amylase level was normal. Abdominal CT scan showed moderate ascites and small bowel loops with a thick and moderately distended appearance. The patient underwent exploratory laparotomy with the initial impression of acute abdomen / small bowel obstruction. During the procedure, a small proximal jejunal volvulus was identified and detorsion was performed.

Three days after the surgery, the patient developed fever, nausea, vomiting and increasing abdominal pain. Repeat abdominal CT scan demonstrated bilateral pleural effusions, moderate ascites, thickening of loops of small bowel, and a horseshoe kidney. Blood count revealed leukocytosis, anemia and worsening thrombocytopenia. The patient was also noted to have deterioration of renal function with BUN / creatinine increasing from 19/1.4 on admission to 75/4.7 with nephrotic-range proteinuria. Further work-up revealed positive serum anti-nuclear antibodies with a titer of 1:320 showing a homogenous pattern, decreased complement levels, positive anti-double stranded DNA antibodies, and positive anti-Smith antibodies. The diagnosis of SLE was made since the patient satisfied seven of the eleven American College of Rheumatology Revised Criteria for Classification of SLE. The patient was started on steroid therapy with dramatic clinical improvement along with resolution of anemia, thrombocytopenia and renal failure.

Discussion and Conclusion: Systemic lupus erythematosus is most prevalent in the 20–40 year age population with a female to male ratio of 9:1. Gastrointestinal complications of SLE include small and large intestinal vasculitis, and ischemic enteritis which may progress to bowel infarction, pancreatitis, inflammatory bowel disease, celiac disease and protein-losing enteropathy.

Intestinal pseudo-obstruction has been very rarely reported in association with systemic lupus erythematosus, and usually in patients with a long duration of the disease and multiple organ involvement. Our patient is unique because of SLE in a man and a two-day history of abdominal complaints and no other associated symptoms suggestive of SLE on initial presentation.

Tenofocir-Related Renal Fanconi Syndrome. Garima Gupta, Erfifida Restrepo, Fred Rosner and Stafford John. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: We report a case of rarely diagnosed Fanconi syndrome associated with tenofovir fumurate, a nucleotide reverse transcriptase inhibitor with anti-HIV therapeutic effect.

Case Report: A 53-year-old HIV-infected woman was referred to our immunology clinic for HIV treatment in January 2005. She had previously received one antiretroviral regimen and was on didanosine (250 mg QD), tenofovir (300 mg QD) and efavirenz (600 mg QHS) since February 2004. She was continued on this antiretroviral regimen. On this visit, she presented with complaints of weakness, fatigue, weight loss of about 20 lbs in the last 3 months and bony pain in both lower extremities. Physical examination showed a body weight of 123 lbs, Blood pressure of 127/78 mmHg with marked muscle atrophy. Her initial laboratory workup was significant for hypokalemia. Her presenting complaints were initially attributed to AIDS. On follow-up visits, she continued to have persistent weakness and fatigue. Further laboratory investigations revealed the following constellation of abnormalities: serum potassium 3.2 meq/L, serum bicarbonate 19 meq/L, serum phosphate 1.1 mg/dL, serum glucose 102mg/dL, serum calcium 8.4 mg/dL, urea 8 mg/dL, serum creatinine 0.9 mg/dL, serum lactic acid 2.4 meq/L. Urinalysis was significant for PH of 7.00, glycosuria (urine glucose level 250 mg/dL, proteinuria (dipstick 1+). Liver function tests showed the serum alkaline phosphate to be increased to 398U/L with a reduced serum albumin level of 3.4 gm/dL.

The presence of hypophosphoremia with mild hypocalcemia along with persistent bony pain in the lower extremities prompted further testing to rule out metabolic bone disease. Serum 25-hydroxy vitamin D level was reduced to 15 ng/mL, intact parathyroid hormone level was increased to 106 pg/mL. Bone densitometry was significant for osteoporosis.

Discussion: Considering this metabolic picture with a non-anion gap metabolic acidosis, normoglycemic glycosuria, proteinuria, hypophosphoremia and mild hypocalcemia, the diagnoses of Fanconi syndrome and vitamin D deficiency were made in March 2006. Antiretroviral treatment including Tenofovir was discontinued and the patient treated with vitamin D, bisphosphonates, potassium phosphate and calcium carbonate. Two weeks later, patient reported to have less in fatigue and weakness with improvement in her exercise tolerance. We anticipate that her electrolyte imbalance will improve with the above interventions.

Summary: This case demonstrates tenofovir-induced Fanconi syndrome with hypokalemia, normoglycemic glycosuria, proteinuria with non-anion gap proximal renal tubular metabolic acidosis.

The mechanism of proximal renal tubular dysfunction is secondary to cellular accumulation through increased entry from human organic anion transporters (hOAT) located on the basolateral side of the tubule and decreased efflux into the tubular lumen mediated by multidrug-resistance-protein (MRP-2). Protease inhibitors can also inhibit MRP-2 thereby decreasing efflux of tenofovir. Patients receiving combinations of tenofovir and protease inhibitors should be closely monitored for the development of proximal renal tubular toxicities.

Conclusion: Nephrotoxity of tenofovir should not be underestimated. This fact becomes more important in view of AIDS patients, where serum creatinine may not increase but timely examination of serum electrolytes and urinalysis will guide the medical staff into making the correct diagnosis.

The Effect of Proton Pump Inhibitors on Serum TSH Levels in Euthyroid Patients on Levothyroxine. Issac Sachmechi, Michael Aninyei, David Reich, Garima Gupta, Francisca Wibowo, Natalia Yurkovetsky, Ebima Okundaye, Chinar Mehta, Jagdesh Kandala, Fred Rosner, and Paul Kim. Department of Medicine, Mount Sinai School of Medicine, Queens Hospital Center, Jamaica, NY.

Introduction: Several medications are known to affect the level of serum thyroid hormone in hypothyroid patients on levothyroxine (L-T4) replacement either by reducing gastrointestinal absorption of L-T4 or increasing its metabolic clearance. Proton pump inhibitors (PPIs) are commonly used; their effect on L-T4 absorption or metabolic clearance in humans is not known.

We have observed an apparent rise in thyroid stimulating hormone (TSH) levels in hypothyroid patients on L-T4 replacement who were later started on PPIs.

Objective: This study was designed to retrospectively examine the effect of PPIs on TSH values in hypothyroid patients with normal TSH levels on L-T4 replacement.

Methods: The data collection was done by retrospective electronic medical record review from the period of December 2002 to August 2005 on patients with hypothyroidism who were on at least 50 mcg daily L-T4 replacements at Queens Hospital Center.

The study group (n=40) patient data was collected by reviewing and randomly selecting euthyroid patients with history of hypothyroidism on stable L-T4 replacement for at least six months who were later started on a PPI. TSH levels were collected prior to and at least one month after the PPI was started.

The control group ($n=71$) patient data was collected by reviewing TSH levels among randomly selected euthyroid patients with history of hypothyroidism on stable L-T4 therapy and not on a PPI during the same period as the study group's data was being examined.

The statistical analysis was done by comparing the mean change in TSH level in each group using the paired test (SAS 6.2 Version).

Results: In the study group, the mean increase in TSH level, 1.3 mIU/mL ± 0.63, was statistically significant ($p < 0.05$). In the control group, the mean change in TSH level, 0.007 mIU/mL ± 0.06, was not statistically significant ($p= 0.95$).

Discussion: The results of the study showed that the use of PPIs in hypothyroid patients on L-T4 replacement significantly affect the level of serum TSH. In animal studies, PPIs were found to increase metabolic clearance of L-T4 by enhancing the activity of the enzyme, L-T4 glucuronyltransferase, that is responsible for glucoronidation of thyroxine. We assume this is the most likely mechanism also in humans, although suppression of gastric acid secretion by PPIs might affect the absorption of L-T4.

Conclusion: To our best knowledge, this is the first study in humans with hypothyroidism demonstrating the effect of PPIs on the metabolism of thyroid hormone. PPIs should be added to the list of medications affecting the level of thyroid hormone in hypothyroid patients treated with L-T4 replacement. Hypothyroid patients with normal TSH values on L-T4 replacement will need additional thyroid function testing following the treatment with PPIs and may need adjustment of L-T4 dose.

Unusual Onset of Acute Rheumatic Fever. Ebima Okundaye, Saurabh Chhabra, Elena Korniychuk, Jean–Louis Dupiton, Fred Rosner, and Adriana Abrudescu.Department of Medicine, Queens Hospital Center, Mount Sinai School of Medicine, Jamaica, NY.

Introduction: Acute rheumatic fever is an immunological sequel of streptococcal sore throat infection. It is a common pathology in children and young adults. It rarely occurs above middle age. There are rare reports of its occurrence in the elderly population. The symptoms usually arise within 1 – 4 weeks after the streptococcal sore throat infection.

Case Report: A 67-year-old woman presented with complaints of malaise, low-grade fever, migrating joint pains and rash of 3 weeks duration. The fever was low grade, not associated with chills, but no temperature was taken at home. The joint pains initially started on the right wrist but later migrated to the left wrist and both ankles. The pain was associated with swelling and warmth and rash over the joints. The patient had associated lethargy and weakness.

The patient gave a history of hypertension, hyperlipidemia and osteoporosis. She had a recent vacation in Mexico 4 months prior where she developed sore throat associated with diarrhea. Both were treated symptomatically and resolved after one week. No antibiotics were given. The patient lives with a daughter and grandchildren.

Physical examination showed an obese woman with marked conjunctival injection, grade -1 leg edema and tenderness in the left wrist and both ankles on movement. There was an erythematous skin rash on the involved joints that blanched on pressure application. Heart auscultation was significant for a grade -1 diastolic murmur over the mitral area.

The patient had an increased white blood cell count with marked neutrophilia. Liver function tests revealed markedly elevated enzymes; erythrocyte sedimentation rate and C-reactive protein were both elevated. Though beta streptococcal throat culture was negative, the serum streptozyme titer was 1:400, and an antistreptolysin -O (ASO) titer was 1:1097. Anti-nuclear antibodies and Rheumatoid factor were both negative. EKG was unremarkable and there was trace protein in the urine.

The patient was diagnosed and managed for acute rheumatic fever. Aspirin and benzathine penicillin stat dose were given two days after admission. Her symptoms improved, as did the physical findings. The patient was discharged on the fifth day after admission.

Discussion: Acute rheumatic fever is an antibody-mediated reaction to streptococcal infection; it is characterized by specific of symptoms and signs. The modified Jones criteria require any two of the major criteria of carditis, erythema marginatum, subcutaneous nodules, migratory polyarthritis and chorea; or one of the major criteria and two minor criteria such as elevated ESR, C-reactive protein, prolonged PR interval, arthralgia and fever, in addition to evidence of beta streptococcal infection. Our patient had the major criterion of migratory polyarthritis and two minor criteria of elevated ESR and fever, in addition to evidence of streptococcal throat infection in that the serum streptozyme and ASO titers were increased.

Summary and Conclusion: The syndrome of acute rheumatic fever is common in children due to the high proliferation of antibodies in that population. The most important complication of streptococcal infection is rheumatic heart disease. Few case reports have described rheumatic fever in the adult population. Perhaps, due to the mature differentiation of the immunoglobulin lineage in this age population at the time of streptococcal sore throat infection. This diagnosis should be considered in patients with polyarthritis in the elderly age group. This case is unique not only in terms of the late age of occurrence but the prolonged latent period between the streptococcal infection and the onset of the immune-mediated acute rheumatic fever.

Use of Early Aggressive Therapy in the Management of Life-Threatening Microscopic Polyangitis: A Succesful Approach. Keside Amaechi, Karen Mrejen-Shakin, Robert Murithi, and Adriana Abrudescu. Department of Medicine, Queens Hospital Center, Mount Sinai School of Medicine, Jamaica, NY.

Diffuse alveolar hemorrhage is characterized by bilateral alveolar infiltrates on chest radiograph, iron deficiency anemia, and hemoptysis. Diagnosis is confirmed by fiberoptic bronchoscopy revealing increasing amounts of red blood cells and hemosiderin-laden macrophages. Antineutrophil cytoplasmic antibodies (ANCA) related small vessel vasculitis commonly present as a rapidly progressive glomerulonephritis and alveolar capillaritis. We report a case of a patient with perinuclear-ANCA positive miroscopic polyangitis who presented with life-threatening pulmonary and renal hemorrhage successfully managed by early treatment with pulse dose corticosteroids, plasmapharesis and cyclophosphamide.

Case Report: A 55-year-old male from Haiti with a past medical history of well-controlled diabetes and hypertension presented to the Emergency Department with complaints of urinary urgency and dry cough for about one week. Urinalysis showed microscopic hematuria and he was told to follow up with his doctor. One week later, he came to our Emergency Department complaining of dry cough with shortness of breath and "pink urine." Vitals were stable. Chest radiograph showed bilateral alveolar pulmonary infiltrates, and serum chemistry now revealed renal insufficiency, (BUN 58 mg/dL, creatinine 6.9 mg/dL). While in the Emergency Department he spiked to 101.° F. He now coughed up large amounts of bright red blood with large clots, and had gross hematuria. The patient became lethargic and hypoxic with a room air saturation of 68%. He was rapidly intubated and admitted to the intensive care unit. Repeat chest radiograph showed significant progression of alveolar infiltrates. On 100% oxygen and low tidal volumes the arterial blood gas was 7.38/40/81. Due to the life threatening hypoxia, broad-spectrum antibiotics, pulse dose intravenous corticosteroids, plasma exchange transfusion, and cyclophosphamide were started within 24 hours. Bronchoscopy confirmed diffuse alveolar hemorrhage. Serum ANA and anti-glomerular basement antibody were negative. P-ANCA (antimyeloperoxidase) was positive (100 U/mL). Kidney biopsy revealed crescentric glomerulonephritis with pauci-immune deposits on electron microscopy, confirming the diagnosis of microscopic polyangitis. Corticosteroids were continued and the patient required dialysis. The patient's oxygenation improved and he was successfully extubated. The patient was discharged from the hospital on low dose oral corticosteroids and off dialysis.

Discussion: In the United States, the annual incidence of microscopic polyangitis is 3 cases per one million persons. It is an autoimmune disease consisting of a necrotizing vasculitis of the small vessels, typically arterioles, venules and capillaries. Several organ systems may be affected but the usual cause of death is pulmonary capillaritis and hemorrhage. Less common presentations include rashes (palpable purpura), gastrointestinal bleeding, myocardial infarction, congestive heart failure, and retinal hemorrhages. Microscopic polyangitis may present indolently, or as a life-threatening emergency. It is difficult to prognosticate which patients will survive.

Conclusion: With adequate treatment, 75% of patients with microscopic polyangitis will be alive after 5 years, and most patients are on dialysis. The timing of treatment may be the single most important clinical determinant of mortality, and renal failure. Therefore, in patients who present with life-threatening pulmonary-renal syndrome, we advocate early aggressive treatment with antibiotics, plasmapharesis and immunosuppressive drugs.

INFORMATION FOR AUTHORS

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Introduction

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Neuropsychiatry

Neurology and psychiatry began as a unified specialty attempting to provide objective assessment of behavior and characterization of the underlying central nervous system biology. Over time the two emerged and drifted apart, at the expense of losing a coordinated approach to managing the complex relationship between the brain and behavior. More recently, better imaging techniques have improved our understanding of the neurobiological basis of psychiatric disorders; this in turn has highlighted the collaborative effort needed between the two specialties in order to maximize our ability to treat and manage neuropsychiatric conditions.

It was with great pleasure that we embraced the challenge to edit this issue on neuropsychiatry for the *Mount Sinai Journal of Medicine*. Dr. Sano is a neuropsychologist involved in designing and conducting clinical trials for neurodegenerative diseases, including Alzheimer's and Parkinson's. She has studied women's attitudes about prevention of memory loss and measuring quality of life. Dr. Riggio is a neurologist and a psychiatrist with a strong interest in the interface between psychiatry and neurology. In particular, she is interested in the psychiatric manifestations of seizure disorders and other neurologic diseases. She has recently edited an issue on neuropsychiatry for the journal *Psychiatric Clinics of North America* and has organized courses for both neurology and psychiatry house staff on the interface of both fields.

This issue begins with an article by Dr. Elder, providing a research update on neuropsychiatry. This article offers a historical perspective and a comprehensive review of neurogenesis in the mammalian brain, with implications for future treatments. Next is a chapter from Dr. Charney, our Dean for Academic and Scientific Affairs, and his collaborators, on the neurobiology of fear and anxiety disorders. It provides an understanding of pathways involved and previously unknown peptide systems with therapeutic potential. Dr. Byne presents a review of disorders of sexual differentiation along with a framework to help us understand the biological substrates of gender identity.

Drs. Riggio and Rowan provide a review of the psychiatric manifestations of seizures disorder, its clinical features, electrodiagnostic changes, diagnostic challenges, and guidelines for treatment. Drs. Sano and Aloysi describe a range of cognitive and affective disturbances in women through menopause and review the neurobiology that underlies treatment options.

There are also articles on cognitive and behavioral disturbances that appear in neuropsychiatric disorders, including two excellent reviews of specific conditions of the elderly, one by Dr. Nassisi and colleagues, on the management of delirium in the elderly patient, and one by Drs. Grossman and Bergmann on the range of dementias. Drs. Bowie and Harvey provide a comprehensive review of schizophrenia as a neuropsychiatric condition, with a focus on cognitive dysfunction.

An article on the neuropsychiatric consequences of brain injury, provided by Dr. Gordon, a professor of rehabilitation medicine, and his colleagues, includes guidelines for clinical assessment addressing both cognitive and psychiatric manifestations. Finally, a review of the neuropsychiatric consequences of cerebral vascular lesions is provided by Dr. Levine, an expert in the treatment and management of stroke, and Dr. Chemerinski, a psychiatrist.

It was our goal to combine our various interests and perspectives in research and clinical practice, thus providing an overview of the field of neuropsychiatry. Our hope is to provide the reader with insightful perspectives on the controversies and challenges we are confronted with and to inspire and promote further collaborative efforts between basic scientists and clinicians in this growing field.

Research Update:

Neurogenesis in Adult Brain and Neuropsychiatric Disorders

Gregory A. Elder, M.D., Rita De Gasperi, Ph.D., and Miguel A. Gama Sosa, Ph.D.

Abstract

Until recently neurogenesis in mammals was considered to occur only during the embryonic and early post-natal periods and to have no significant role in the adult nervous system. However, it is now accepted that neurogenesis occurs in two brain regions in adult mammals, namely, the hippocampus and olfactory bulb. In both regions new neurons arise from a resident population of neural progenitor cells that are maintained throughout adult life.

Hippocampal neurogenesis is required for some types of hippocampal-dependent learning. Many factors enhance hippocampal neurogenesis including hormones, growth factors, drugs, neurotransmitters, and physical exercise as well as learning a hippocampal-dependent task. Other factors suppress hippocampal neurogenesis; these include aging, stress, glucocorticoids and stimuli that activate the pituitary/adrenal axis. Recently much attention has focused on the relevance of hippocampal neurogenesis to the pathophysiology and treatment of mood disorders. Indeed all major pharmacological and non-pharmacological treatments for depression enhance hippocampal neurogenesis and suppressing hippocampal neurogenesis in mice blocks behavioral responses in some antidepressant-sensitive tests. Altered hippocampal neurogenesis may also play a pathophysiological role in neurodegenerative disorders such as Alzheimer's disease. How much neurogenesis occurs normally in other brain regions is unclear. Neural progenitors are found throughout the neuraxis including both neurogenic and non-neurogenic regions. When cultured *in vitro* or isolated and transplanted back into neurogenic brain regions, these cells can differentiate into neurons, although in their *in situ* location they seem to behave as lineage-restricted glial progenitors. The environmental cues that limit the potential of progenitor cells in non-neurogenic brain regions are unknown. However, an emerging view is that astrocytes, a subset of which also functions as neural progenitor cells, are critical in regulating the local environment.

After transplantation into adult brain, neural stem cells are capable of surviving and differentiating into both neurons and glial cells, offering hope that stem cell therapy may be utilized to treat a variety of neurological and perhaps psychiatric disorders. The widespread existence of endogenous neural progenitors even in non-neurogenic brain regions also offers hope that the potential of these cells may be harnessed to repair cellular injuries caused by injuries such as stroke, trauma or neurodegenerative diseases. While obstacles remain to both approaches, stem-cell-based therapies remain an area of intense research interest.

Key Words: Alzheimer's disease, bromodeoxyuridine, depression, hippocampus, major affective disorders, neural progenitors, neural stem cells, neurodegenerative diseases, neurogenesis, stem cell therapy.

Historical Perspective

In MAMMALS, NEUROGENESIS, i.e., the production of new neurons, has until recently been considered to occur only during the embryonic and early post-natal periods and to have no significant role in the adult brain. Indeed, Santiago Ramon Y Cajal, who first described neurons using the technique of Golgi staining, concluded that neurons were only generated during prenatal development, and this "no new neuron" doctrine has prevailed until recently. Various reasons accounted for the persistence of this view, including the lack of mitotic figures in mature neurons, the fact that neuronal numbers in adult brain appear to be stable or declining in number with age as well as a generally more "hard wired" view of the adult brain.

Following the introduction of [^{3}H]-thymidine labeling, scattered reports, in particular the studies of Altman (1), described labeling of neurons in both cortical and subcortical regions of adult rodents. However, the number of cells labeled was low, and using the morphological criteria available at the time, doubt remained as to whether the labeled cells were actually neurons. In the 1980s the question of neurogenesis in adult brain was extensively reexamined using [^{3}H]-thymidine labeling in non-human primates with the conclusion that neurogenesis was confined to embryonic and early post-natal life and that there is no neurogenesis in adult brain (2).

During the last 10 years this "no neuron doctrine" has had to be revised to acknowledge that at least "limited" neurogenesis occurs normally in selected regions of adult mammalian brain and that neurogenesis may be stimulated in these as well as other regions in response to injury. This modified view has come about in part because of technical

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improvements in methods available for labeling dividing cells as well as the availability of a broad array of cell-type-specific markers that allowed cells to be identified on other than morphological grounds. This concept has also been bolstered by the finding that a resident population of neural progenitor cells exists in adult brain, obviating the need for mature neurons to become mitotic.

Neurogenic Brain Regions

It is now accepted that neurogenesis occurs in two brain regions in adult mammals, namely, the hippocampus and olfactory bulb (3). Neurogenesis in both regions has been demonstrated in the brains of rodents, non-human primates and humans. In the hippocampus, new granule cell neurons arise from neural progenitor cells located within the hippocampus itself in a region known as the subgranular zone (see below). By contrast the neural progenitors that give rise to new neurons in the olfactory bulb reside in the region around the anterior lateral ventricle termed the subventricular zone. Within the subventricular zone neural progenitors proliferate throughout life before differentiating and migrating through a tract known as the rostral migratory stream, ultimately giving rise to new granule cell neurons and a special type of interneuron in the olfactory bulb. Neurogenesis in the olfactory bulb in rodents has been extensively studied experimentally. Since it has less direct clinical relevance it will not be discussed here further. However, extensive reviews on this subject are available elsewhere (4, 5).

In contrast to hippocampus and olfactory bulb, other brain regions including the cerebellum, brainstem, basal ganglia, and spinal cord appear to be non-neurogenic. While neurogenesis may be stimulated in some of these regions by injury, it remains unclear how much if any constitutive neurogenesis occurs in these regions normally. The issue of neurogenesis in neocortex remains controversial, as discussed below. In the peripheral nervous system (PNS), only the olfactory neuroepithelium of the nasal mucosa has been demonstrated to be neurogenic in adults (6).

How Neurogenesis Is Studied in Adult Brain

Mature neurons are post-mitotic cells. By contrast, neural progenitor cells periodically divide. Therefore, the behavior of neural progenitors can be tracked by labeling them with nucleotide analogs that become incorporated into the DNA of dividing cells. Once incorporated the nucleotide analog remains within the progeny during subsequent rounds of cell division. Historically [^{3}H]-thymidine was the first analog widely used. However, the [^{3}H]-thymidine signal penetrates thick tissue sections poorly and is difficult technically to combine with immunohistochemical labeling. It has now been largely replaced by bromodeoxyuridine (BrdU). BrdU is a thymidine analog that once incorporated into dividing cells can be labeled by immunohistochemical staining, which can be combined with cell-type-specific markers, allowing more precise identification of neuronal and non-neuronal cells. Examples of BrdU-labeled cells in the hippocampus of an adult mouse brain are shown in Fig. 1. Labeling with cell-type-specific markers combined with BrdU immunohistochemistry is shown in Fig. 2.

Using BrdU labeling, it is possible to measure three parameters of neural progenitor behavior. Typically several doses of BrdU are given over a 48-hour period. If the animal is sacrificed at the end of this labeling period and the number of BrdU labeled cells in the hippocampal subgranular zone are counted, an index of neural progenitor proliferation rate can be established. If the same dosing schedule is followed, but the animal is allowed to survive for several weeks, the number of BrdU labeled cells remaining in the dentate gyrus can be counted, giving an index of the fractional survival of the initially labeled progenitor population. Furthermore, the phenotype of surviving BrdU-labeled cells can be determined by dual immunocytochemical staining, allowing the fraction cells that became neurons or glial cells to be determined. Finally, by multiplying the number of surviving cells by the fraction of those cells that acquired neuronal markers the number of the new neurons produced from the initially labeled BrdU population can be calculated.

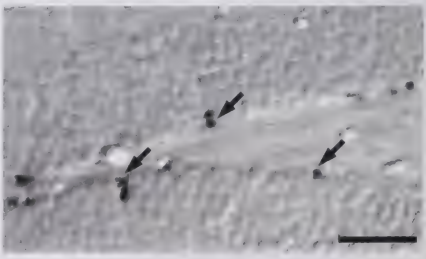

Fig. 1. An example of immunoperoxidase staining for bromodeoxyuridine (BrdU) in the hippocampus of an adult mouse is shown. Arrows indicate examples of BrdU-labeled cells in the subgranular zone.

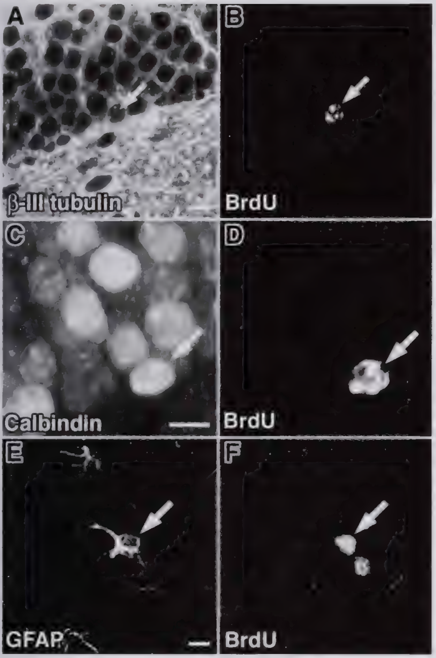

Fig. 2. Confocal laser-scanning microscopy images of bromodeoxyuridine (BrdU)-labeled cells 4 weeks after the last BrdU injection. Cells are shown co-labeled with BrdU and the neuronal markers β-III tubulin **(A–B)** or calbindin **(C–D)** or with the astrocyte marker GFAP **(E–F)**. Arrows in each set of panels point to co-labeled cells. Scale bars: 10 μm.

While extensively utilized to study progenitor cell fate, the general strategy has limitations. First, BrdU labeling will not permanently mark highly proliferative cells since the signal will be diluted with each round of cell division until ultimately it is no longer detectible. In addition, BrdU's limited bioavailability after injection may be no more than two hours in the adult brain (7), meaning that repeated injections must be given to quantitatively label adult progenitor cells, which have a cell cycle of ≈ 25 hrs (7). Doses must be further adjusted to capture the population of slow-cycling progenitor cells (8).

Indeed the true efficiency of BrdU labeling is unknown and recent studies have suggested that the most commonly used doses of BrdU fail to label all dividing cells (7). The issue of labeling sensitivity is of particular concern in regions where basal levels of neurogenesis may be low at any given time but significant over a lifetime. Concerns have also been raised about BrdU's possible toxic effects on progenitor cells and even its specificity for dividing cells since cells undergoing DNA repair may also be labeled. Indeed, mature neurons may reenter the cell cycle prior to undergoing apoptosis. Concerns have also been raised about the specificity of some of the widely utilized cell-type-specific markers. Despite the fact that BrdU labeling has become the industry standard for studies of neurogenesis in the adult nervous system limitations remain which, in particular, limit BrdU's usefulness for following progenitor cell behavior over long time periods in adult brain.

The Fate of BrdU-Labeled Cells in Adult Mouse Hippocampus

Using a labeling protocol as described above, at the end of the injection period several thousand BrdU-labeled cells can be detected in the hippocampal subgranular zone of a young adult mouse. At four weeks after injection this number is reduced to about one-third of the original. Most of the two-thirds of cells that are lost are presumed to undergo programmed cell death through apoptosis although some loss through label dilution is difficult to exclude. Of the BrdU-labeled cells that remain approximately half express neuron-specific markers, another 10–15% glial-specific markers and the ≈35% remaining have no identifiable phenotype. From such studies, the rate of new neuron generation in young adult mice or rats has been estimated to be from 1.5% (9) to 6% (7) of the total granule cell population per month, amounting to the hippocampus of a three-month-old mouse producing about one new neuron per day per 2,000 existing granule cells (9). Since at this age an adult mouse hippocampus contains ≈250,000 granule neurons, the hippocampal granule cell layer could theoretically turn over in about four months. Whether this indeed happens and whether all granule cells are equally likely to be replaced is unknown.

Origins of Neural Progenitors in Adult Brain

Neural progenitors in regions such as the hippocampal subgranular and subventricular zone are generally thought to represent a resident population of cells that is established at birth and maintained throughout life by a combination of symmetric and asymmetric cell divisions that both renew the progenitor population and generate daughter cells that adopt neuronal or glial fates. The designation of a cell as a "stem cell" implies both the capacity for self-renewal as well as multipotentiality, in the brain implying the ability to give rise to progeny with both neuronal and glial fates. Within the population of BrdU-labeled cells in the hippocampal subgranular zone, there is probably a population of true stem cells. However, since there are no markers that will differentiate whether an individual cell is a stem cell or has adopted a more restricted fate, BrdU-labeled cells in the subgranular zone are frequently referred by the more generic term "neural progenitor."

A peripheral origin would seem to constitute the only major alternative to the "resident since birth view." Notably, neural progenitor cells in both the hippocampal subgranular zone and the subventricular zone exist in close proximity to blood vessels in what has come to be referred to as a vascular niche (10). Why neural progenitor cells reside in a vascular niche is unclear, although reasonable speculations include that blood vessels may condition the niche with factors that help neural progenitors maintain their proliferative and undifferentiated nature; and recent *in vitro* studies have supported a role for soluble factors secreted by endothelial cells in maintaining neural stem cells in an undifferentiated state (11). However, a vascular niche might also imply that neural progenitor cells are derived from outside the central nervous system (CNS). Indeed, it is now well accepted that a circulating population of stem cells exists in adult blood and that at least under some *in vitro* conditions non-CNS stem cells may transdifferentiate into neurons (12). Whether transdifferentiation occurs *in vivo* is controversial and no studies to date have provided evidence that circulating stem cells repopulate the progenitor niches in the hippocampus and subventricular zone.

Functional Significance of Neurogenesis in the Adult Hippocampus

If new neurons are generated in adult brain, what might their function be? An immediate question is, do the new granule cell neurons in the hippocampus make functional connections? Hippocampal granule neurons are part of a synaptic circuit that receives input from the entorhinal cortex and sends projections to the pyramidal neurons in the CA3–CA1 region of the hippocampus. If newly generated granule neurons are to participate functionally in these circuits, they must send axonal projections into the mossy fibers that carry granule cell output to the hippocampal pyramidal cells. Indeed, retrograde tracer studies using injections into the terminal fields of the mossy fibers have established that newly born BrdU-labeled neurons in the granule cell layer do send axonal projections to the pyramidal cell layers (13).

Since the hippocampus is best known for its role in learning and memory, one immediate question is whether neurogenesis might facilitate hippocampal-dependent learning. A general correlation does exist within inbred strains of mice between higher rates of neurogenesis in adult hippocampus and learning potential, as judged by the Morris water maze (14). To test this hypothesis experimentally Shors et al. (15) abolished hippocampal neurogenesis by treating adult rats with the DNA-methylating agent methylazoxymethanol acetate (MAM). They then asked whether disrupting hippocampal neurogenesis would impair performance in a test in which an eye blink elicited by an electrical stimulus was conditioned to occur in response to a white noise. In one version of the test, known as "delayed conditioning," the white noise and the periorbital stimulation (or unconditioned stimulus) overlap temporally and learning does not require an intact hippocampus. In the second version, known as "trace conditioning," a gap is present between the unconditioned and conditioned stimulus, and an intact hippocampus is required for leaning to occur. Interestingly, treatment with MAM impaired the hippocampal-dependent but not the hippocampal-independent leaning, arguing that hippocampal neurogenesis is involved in formation of trace memories.

Agents such as MAM are highly toxic and could be exhibiting effects on non-dividing cells, a confounding variable that is difficult to ever completely exclude. However, arguing against a general toxic effect of MAM, there was no change in hippocampal volume, cell numbers or long-term potentiation in the MAM-treated animals. In addition, if hippocampal neurogenesis was allowed to recover, leaning in the hippocampal-dependent task recovered as well. Most recent studies continue to support the notion that hippocampal neurogenesis plays a role in at least some forms of hippocampal learning and memory.

Factors that Affect Hippocampal Neurogenesis in Adult Brain

Many factors affect hippocampal neurogenesis, including hormones, growth factors, drugs and neurotransmitters (3). Not only may hippocampal neurogenesis be required for some types of learning, but learning a task can also stimulate hippocampal neurogenesis (16). Environmental manipulations can also enhance hippocampal neurogenesis. For example, environmental enrichment which consists of switching animals from housing in standard laboratory cages to an environment with increased opportunities for social interaction, exploration and physical activity produces a range of morphological and behavioral changes in rodents including stimulating hippocampal neurogenesis (17). Physical exercise enhances hippocampal neurogenesis quite possibly by stimulating the systemic production of insulin-like growth factor 1 (18). Estrogen stimulates hippocampal neurogenesis and the rate of hippocampal neurogenesis is increased during phases of the estrus cycle when estrogen levels are high (19). Besides increasing longevity, dietary restriction also enhances hippocampal neurogenesis (20).

Other factors suppress hippocampal neurogenesis. In general, glucocorticoids or any stimulus that activates the pituitary/adrenal axis suppresses hippocampal neurogenesis. Activation of the pituitary/adrenal axis may at least partly account for the consistent effects of a variety of stress paradigms on suppressing hippocampal neurogenesis (21). Stress and pituitary/adrenal activation may also account for the suppression of hippocampal neurogenesis seen with social isolation (22) and lower social hierarchy in rodents in which hippocampal neurogenesis is decreased in subordinate males (23). Hippocampal neurogenesis also decreases with aging (24) and may be impaired in pathological states that provoke some types of inflammation (25).

Neurogenesis as a Response to Injury

In general, neurogenesis is stimulated by injuries to the hippocampus. Insults including ischemia (26), seizures (27) and direct excitotoxic lesioning of the hippocampal granule cell layer (28) all increase neural progenitor proliferation. Lesioning the hippocampus indirectly by removing its afferent input from the entorhinal cortex also stimulates neurogenesis (29).

Injury may also stimulate neurogenesis outside the hippocampus. Occlusion of the middle cerebral artery in rats, for example, in addition to enhancing hippocampal neurogenesis, induces neural progenitors in the subventricular zone to migrate into the cerebral cortex and striatum (30). What remains unclear is the degree to which such activation results in actual repair and the reestablishment of functional connections. While the answer to this question is not fully known, targeted injuries to select neocortical layers in mice has been shown to stimulate the appearance of BrdU-labeled cells within the neocortex (31), reflecting cell labeling induced within the neocortex itself as well as migration of BrdU-labeled cells from the subventricular zone (31). Some of these labeled cells differentiate into neurons and, most interestingly, some fraction of them send projections to the thalamus and reestablish corticothalamic projections. While these studies do not establish full functionality, they do offer hope that following brain injuries more plasticity exists in adult brain than might have been expected and that the capacity exists to reestablish functional connections between brain regions.

Hippocampal Neurogenesis and Depression

Hippocampal neurogenesis might at first be thought to have little relevance to major affective disorders. Yet recently, much attention has been focused on hippocampal neurogenesis in relation to the pathophysiology and treatment of mood disorders. Interest was initially stimulated by the observation that all major pharmacological and nonpharmacological treatments for depression enhance hippocampal neurogenesis (32). Indeed, clinically effective agents including selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors, tricyclics, lithium, and monoamine oxidase (MAO) inhibitors enhance hippocampal neurogenesis. Similar effects are also seen with newer agents predicted to have antidepressant efficacy, including rolipram (a type IV phosphodiesterase inhibitor), substance P (NK1 receptor) antagonists, group II metabotropic glutamate receptor antagonists and AMPA (a-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid) receptor potentiators. The effects are specific in that non-antidepressant agents, such as haloperidol, do not consistently enhance hippocampal neurogenesis. Interestingly, the time course of the effects that agents such as fluoxetine have on neurogenesis are delayed in a manner consistent with the known delay in the clinical efficacy of the drugs. Nonpharmacological manipulations such as electroconvulsive shock therapy (ECT) also increase neural progenitor proliferation and neurogenesis. Indeed, of all antidepressant treatments tested to date, only one putative therapy, transcranial magnetic stimulation, may not affect hippocampal neurogenesis (32).

In major depression, it has been hypothesized that neuronal systems may be unable to respond to stressful stimuli with appropriate adaptive plasticity (33). Neurogenesis may be seen as one form of adaptive plasticity. Various acute and chronic physical or psychosocial stress paradigms all reduce neural progenitor proliferation and neurogenesis in the hippocampus of adult animals (34, 35). Stress-induced reductions in neural progenitor proliferation in the hippocampus can also be reversed with antidepressant treatments including tricyclics, SSRIs and NK1 receptor antagonists (34, 36, 37). These effects have been seen in models of psychosocial stress (36) and learned helplessness (34). Thus, one current working hypothesis is that reduced neural progenitor proliferation leads to decreased hippocampal neurogenesis and that reversing or blocking this decrease may be one way that antidepressant treatments exert therapeutic effects.

Admittedly, it was well known before the effects of antidepressants on neurogenesis were discovered that stress adversely affects the hippocampus in other ways, including producing atrophy and reduced dendritic arborization of CA3 pyramidal neurons (38), and that some of these effects can be reversed by antidepressants (38). Indeed, the degree to which effects on hippocampal neurogenesis underlie the therapeutic benefits of antidepressant treatments remains to be determined and several recent commentaries have summarized arguments, both pro and con, on this issue (39–41).

However, recent studies by Santarelli et al. (42) in mice seem to strongly support the notion that hippocampal neurogenesis plays some role in the actions of antidepressant compounds. In these studies, hippocampal neurogenesis was blocked with fractionated radiation directed to the hippocampus. Mice were then tested in an antidepressant-sensitive behavioral test called the novelty-suppressed feeding test, in which following fasting, the time that it takes for a mouse to eat in a novel environment is measured. The test is considered a measure of anxiety since anxiolytic drugs reduce feeding latency. It is also considered a measure of antidepressant effect since commonly used antidepressant compounds have a similar effect. Reducing neural progenitor proliferation blocked the responses of mice to both fluoxetine and imipramine in the novelty-suppressed feeding test, arguing that hippocampal neurogenesis is necessary for the actions of antidepressants in this test.

As with cytotoxic agents, interpretation of such studies is confounded by whether radiation may be affecting factors other than hippocampal neurogenesis since in these studies other regions including the hypothalamus and amygdala, which might also be involved in mediating antidepressant effects, were included in the irradiated area. While such effects are difficult to completely exclude, no changes were found in brain histology, numbers of granule cell neurons or hippocampal long-term potentiation. A variety of neuroendocrine responses were also normal and a separate behavioral test, the cued fear conditioning test, which is regarded as a test of amygdala function, were intact. Collectively, these studies strongly argue that at least some of the effects of antidepressants are mediated through their influence on hippocampal neurogenesis.

How antidepressants exert their actions is not completely understood. At the cellular level, antidepressants seem to principally increase the proliferation rate of neural progenitors without effecting fractional survival rate or the rate at which surviving cells differentiate into neurons (32). Thus antidepressants probably enhance neurogenesis by increasing the size of the progenitor pool. Although effects have been principally studied *in vivo*, fluoxetine (43) and lithium (44) have been noted to increase cell proliferation *in vitro* as well.

At the molecular level it is not known how antidepressants influence neural progenitor proliferation. As noted above, stress adversely affects hippocampal function at least in part through hyperactivity of the pituitary/adrenal axis and hypersecretion of glucocorticoids (45). A connection between activity of the glucocorticoid system and excitatory amino acids has been suggested by the finding that cortisol-induced decreases in neural progenitor proliferation can be prevented by administration of the *N*-methyl-D-aspartate (NMDA) antagonist MK-801 (45).

Antidepressants affect additional pathways that may be relevant to their effects on hippocampal neurogenesis, the best studied of these being the interactions of antidepressants with the brain-derived neurotrophic factor (BDNF) signaling pathway (46). BDNF is of interest since both BDNF mRNA and protein increase in response to antidepressant treatments and BDNF is one of a number of growth factors that enhance hippocampal neurogenesis. BDNF administered exogenously to brain either intraventricularly or intrahippocampal mimics the effects of antidepressants in a number of behavioral models of depression. Stress also downregulates BDNF levels and antidepressants reverse this effect.

Thus, by impacting both the glucocorticoid and BDNF pathways, antidepressants intersect with two major pathways that also regulate hippocampal neurogenesis. That these are the only pathways, however, seems unlikely: indeed, recent microarray and proteomic studies of antidepressant-treated animals have identified several other potential targets for antidepressant actions that might also impact hippocampal neurogenesis (47, 48)

Hippocampal Neurogenesis and Alzheimer's Disease

Alzheimer's disease (AD) is a degenerative disorder of the brain characterized clinically by progressive loss of memory and other cognitive skills. Its pathological hallmarks include neuronal and synaptic loss, amyloid plaques, and neurofibrillary tangles. While most cases occur sporadically, the disease is inherited in some families in an autosomal dominant fashion. These familial AD (FAD) cases share the identical clinical and pathological features as sporadic AD except for their generally earlier age of onset (49). Mutations in the amyloid precursor protein as well as the presenilin genes have been found to cause early onset FAD (49).

Several studies have found that neurogenesis is impaired in the hippocampus of transgenic mice expressing presenilin 1 FAD mutants (50–52). Decreased progenitor proliferation has also been noted in mice expressing FAD mutations in the amyloid precursor protein (53). The molecular basis for this impairment is unknown, although Ab peptide, which is overproduced in FAD mutant brain and is the principle component of senile plaques, may be directly toxic to neural progenitor cells (54). At the cellular level, the presenilin-1 FAD mutants seem to primarily reduce the fractional survival of BrdU-labeled neural progenitors without decreasing total granule cell numbers, suggesting that the FAD mutant's primary effect is to alter the kinetics of new neuron production, in essence making the hippocampus in the FAD mutant generate more neural progenitors in order to maintain the same number of granule cell neurons (50).

Whether a similar impairment occurs in human FAD cases or in the more common sporadic disease is not known. One study has reported that the number of neurons expressing immature neuronal markers such as doublecortin, polysaturated nerve cell adhesion molecule (PSA-NCAM) and TUC-4 (TOAD [Turned On After Division]/Ulip/CRMP) are increased in the hippocampal granule cell layer of sporadic human cases (55). The authors of this study interpreted their findings as indicating that neurogenesis was increased in the hippocampus in Alzheimer's disease. However, given the lack of any method for tracking the fate of these immature neurons and, in particular, whether they ever progress to become mature neurons, these results could also be interpreted as showing that in AD hippocampal neurogenesis is blocked at the stage of immature neuron generation.

Of direct clinical relevance is whether impaired neurogenesis might contribute to cognitive dysfunction in AD. Pointing to a possibly relevant role, the hippocampus is pathologically affected early in AD with pyramidal cell loss and disruption of perforating path connections from the entorhinal cortex. Granule cell neurons exhibit cytoskeletal changes that are similar to those found in other neurons in AD, possibly impairing neurogenesis. It is also interesting that the rate of hippocampal neurogenesis decreases with aging coincident with age-related memory decline (24) and that age related memory impairments may be improved in rodents following transplantation of immortalized neural stem cells into brain (56). Moreover, factors that positively affect hippocampal neurogenesis, such as estrogen (57), and cognitively stimulating activities (58) may reduce the risk of AD. Yet of the major brain regions ultimately affected by AD pathology, only the hippocampus is currently regarded as neurogenic, and even in the hippocampus, the brunt of the pathology is in the pyramidal neurons, which are currently regarded as non-neurogenic. Thus, whether hippocampal neurogenesis can be considered a legitimate therapeutic target in AD is at present unclear.

Neurogenesis in Non-neurogenic Brain Regions

Discussion of disorders such as AD leads into the broader question of how much neurogenesis continues in regions of the adult brain beyond the hippocampus and subventricular zone/olfactory bulb. Neocortical regions have, for example, long been regarded as non-neurogenic. However, this view was challenged by Gould and colleagues in 1999 (59). Using a combination of BrdU labeling along with neuronal specific markers and retrograde tracers they reported that new neurons are continuously generated during adulthood in the neocortex of non-human primates. However, a latter study by Kornack and Rakic (60) in non-human primates found only glial cell labeling in neocortex and no evidence for neurogenesis. The differing conclusions of these two studies can be reduced to contrasting interpretations of data collected in stacks from a confocal microscope, highlighting how difficult a seemingly simple question can be to resolve. More recent studies have tended to side with Kornack and Rakic on this issue (61).

Separating the Neurogenic from the Non-neurogenic

What may be seen as the relatively limited neurogenic potential of most brain regions in the adult has led researchers such as Steven Goldman to comment that "the brain is generally not friendly to new neurons" (62). Indeed *in vivo*, most "stem"/progenitor cells in the adult CNS seem to behave as lineage-restricted glial progenitors. One might therefore ask if neurogenic progenitors are confined to neurogenic regions. The answer to this question is clearly no. Progenitor cells that can give rise to neurons *in vitro* can be expected to be isolated from the adult hippocampus and subventricular zone, but they can also be isolated from essentially all non-neurogenic regions including the subcortical white matter, striatum and spinal cord.

Indeed, Goldman's group (63) has successfully fluorescence-activated cell sorting (FACS)-sorted adult neural progenitor cells from the temporal lobe white matter of human surgical specimens using the antibody A2B5. These cells formed neurospheres in culture that could differentiate and be induced to express neuronal-specific markers. In addition, they behaved as multipotent stem cells *in vivo* when transplanted into embryonic rat brain, giving rise to both neuronal and glial lineages. While such observations do not prove that multipotent stem cells exist in human temporal lobe white matter *in vivo*, they do indicate that progenitors isolated from white matter have not forgotten how to behave as stem cells.

What then limits the potential of these cells *in vivo*? An evolving view is that it is not an innate property of the progenitors themselves, but rather the environment, that controls their potential. Clues to these environmental controls have come from studies in which neural progenitors isolated from non-neurogenic regions such as the spinal cord were transplanted back into either spinal cord or hippocampus (64). Cells that were transplanted back into their natural home, the non-neurogenic spinal cord differentiated into only glial cells. However, cells that were transplanted into the hilus of the hippocampus integrated into the subgranular zone and began to express neuronal markers, suggesting that in the hippocampus local environmental factors had instructed the transplanted cells to adopt a neuronal fate.

How environmental cues control the potential of resident progenitor cells is unknown. However, emerging evidence points to a central role of astrocytes in determining neurogenic vs. non-neurogenic brain regions. Astrocytes have long been viewed as playing a support role in the CNS, being involved in metabolic support of neurons as well as injury repair. Astrocytes have more recently been recognized to also play a role as neural progenitor cells themselves in both the developing and mature CNS (62, 65). In addition, the major neural stem cell in the subventricular zone in adult brain has been identified as an astrocyte-like cell and a subset of astrocytes in the hippocampal subgranular zone also have stem-cell-like properties (62).

Besides serving as stem cells, astrocytes have also been reported to promote neurogenesis. For example, Song et al. (66) cultured neural progenitors from the adult rat hippocampus with either primary cultures of hippocampal neurons or astrocytes. Interestingly, they found that neural progenitors cultured with neurons assumed an oligodendroglial fate while progenitors cultured with astrocytes were induced to differentiate into neurons. Moreover, the effect depended on the source of the astrocytes. While astrocyte cultures established from hippocampus promoted neurogenesis, astrocytes from spinal cord promoted only glial differentiation. These studies clearly argue that heterogeneity exists in the ability of astrocytes from different CNS regions to promote neurogenesis. What factors determine the regional specification of astrocytes and whether, for example, astrocytes in different brain regions secrete different complements of growth factors is unknown.

Therapeutic Implications

Following transplantation into the adult brain, stem cells are capable of surviving and differentiating into both neurons and glial cells. Stem cell therapy is thus being considered for a variety of neurological and even psychiatric disorders. Replacement strategies typically contemplate injecting neural or embryonic stem cells that may have been partially differentiated *in vitro* into the mature CNS, with the hope that these cells will restore lost function. Some disorders seem more amenable to this approach than others. Parkinson's disease, for example, is considered to be a good target since the cell type that needs to be replaced and its location are well known. Other disorders such as Alzheimer's disease pose greater challenges since the cell types lost are more diverse and the disease ultimately spreads diffusely.

Given the widespread existence of endogenous neural progenitors even in non-neurogenic brain regions, an attractive alternative to transplantation would be to harness the potential of endogenous progenitors to repair cellular injuries. As discussed above, whether this strategy can ever be exploited may well depend on understanding the environmental cues that determine the neurogenic from non-neurogenic.

Yet whether utilizing transplanted cells or endogenous stem cells, other obstacles remain. For example, even if stem cells can be recruited or induced in the correct location *in situ*, a mechanism must be in place to induce differentiation into the correct neurochemical or other phenotype. In addition, neurons in the adult brain exist not just as neurotransmitter pumps, but must be integrated into neuronal circuits, in many cases extending axons over long distances such as the long corticocortical connections that are lost in AD. Additionally, even if axons succeed in growing into appropriate target regions, how readily will new fibers reestablish appropriate connections in the setting of an ongoing neurodegenerative process?

Yet while many obstacles remain, the capacity of engrafted stem cells to function in the adult nervous system and the existence of a resident potential stem cell population in the adult brain continue to raise hope that repair and rejuvenation through stem cell approaches might be possible. As such, neurogenesis in the adult brain can be expected to remain an area of intense research interest for many years to come.

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Neurobiology of Anxiety Disorders and Implications for Treatment

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Abstract

The neurobiology of the anxiety disorders, which include panic disorder, post-traumatic stress disorder (PTSD), and specific phobias, among others, has been clarified by advances in the field of classical or Pavlovian conditioning, and in our understanding of basic mechanisms of memory and learning. Fear conditioning occurs when a neutral conditioned stimulus (such as a tone) is paired with an aversive, or unconditioned stimulus (such as a footshock), and then in the absence of the unconditioned stimulus, causes a conditioned fear response. Preclinical studies have shown that the amygdala plays a key role in fear circuitry, and that abnormalities in amygdala pathways can affect the acquisition and expression of fear conditioning. Drugs such as glutamate *N*-methyl-D-aspartate (NMDA) antagonists, and blockers of voltage-gated calcium channels, in the amygdala, may block these effects. There is also preliminary evidence for the use of centrally acting beta-adrenergic antagonists, like propranolol, to inhibit consolidation of traumatic memories in PTSD. Finally, fear extinction, which entails new learning of fear inhibition, is central to the mechanism of effective anti-anxiety treatments. Several pharmacological manipulations, such as D-cycloserine, a partial NMDA agonist, have been found to facilitate extinction. Combining these medication approaches with psychotherapies that promote extinction, such as cognitive behavioral therapy (CBT), may offer patients with anxiety disorders a rapid and robust treatment with good durability of effect.

Key Words: Phobia, PTSD, panic, reconsolidation, extinction, amygdala, prefrontal cortex, fear, classical conditioning, Pavlov.

Introduction

ANXIETY DISORDERS are the most common type of psychiatric disorders, with an incidence of 18.1% and a lifetime prevalence of 28.8% (1, 2). They account for a $42.3 billion annual cost in the United States, with over 50% of the total sum directed towards nonpsychiatric medical treatment costs (3). According to the National Comorbidity Survey Replication, in a given year, only about 37% of patients with anxiety disorders utilize any form of health services, including visits with psychiatrists (13%), other mental health practitioners (16%), or general medical doctors (24.3%) (4). Patients with anxiety disorders also have a high comorbidity with mood disorders, with up to 90% of patients experiencing some form of depression in their lifetime (5).

Our understanding of anxiety disorders, such as phobias, panic disorder and PTSD, has benefited from research on the neurobiology of fear and fear conditioning. This article will review this research and examine its implications for these anxiety disorders, with a focus on identifying potential therapeutic strategies.

Below is a brief summary of the diagnostic features from the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) for the major "fear-based" anxiety disorders, which have been associated with pathological fear response (6).

Panic disorder (PD) (prevalence: 4.7%) is a syndrome in which a person experiences recurrent and unexpected attacks, of sudden onset and short duration (10 – 15 minutes), which consist of the following symptoms: shortness of breath, palpitations, chest pain, sweating, chills, nausea, trembling, fear of dying or losing control, numbness, and a feeling of detachment or unreality. PD may or may not be accompanied by agoraphobia, an avoidance of situations where a person may feel trapped and unable to escape (e.g., trains, large crowds) (6). **Post-traumatic stress disorder** (prevalence: 6.8%) is a potentially debilitating chronic illness, caused by witnessing or experienc-

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ing a serious traumatic event, in which the person feels a threat to his/her life or the life of others, and experiences intense fear and horror. Typically, patients re-experience the traumatic event (e.g., nightmares, flashbacks), engage in avoidance of stimuli associated with the sentinel trauma (e.g., impaired recall of events related to the trauma, anhedonia, restricted affect), and experience increased autonomic reactivity (e.g., hypervigilance, irritability, insomnia, heightened startle response) (6). **Phobias**, among the most common psychiatric disorders, were previously classified as social phobia, now called **social anxiety disorder (SAD)** (prevalence: 12.1%), or specific phobia. SAD is defined as persistent fear of showing anxiety symptoms when exposed to unfamiliar situations or people and potential scrutiny, which result in humiliation and avoidance. Affected persons show avoidance of such social or performance situations, and when forced, will experience intense anxiety, and possibly even panic attacks (6). **Specific phobias** (prevalence: 12.5%) are marked by a persistent, excessive fear of a specific object or situation (classified as animal type, natural environment type, blood-injection injury type, situational type, and other type). This causes a potentially maladaptive avoidance of the phobic stimulus, and a severe anxiety reaction, such as a panic attack, when exposed to it (6).

Although anxiety disorders present with different symptoms, severity and natural histories, the therapeutic interventions for all these disorder are similar. For PD, the Food and Drug Administration (FDA)-approved medication treatments are either a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine; sertraline; paroxetine or paroxetine controlled release; or venlafaxine XR, a selective serotonin-norepinephrine reuptake inhibitor (SNRI) (7). The other recommended treatment for PD is cognitive behavioral therapy (CBT), or specifically, panic control therapy, a 12-week psychotherapy treatment that involves addressing cognitive distortions, psychoeducation, breathing exercises, progressive muscle relaxation, and progressive exposure (8). Both CBT and medication treatment have been shown to be equally effective, although evidence that combination treatment is better has been disputed. For PTSD, the evidence-based, first-line treatments are SSRIs (sertraline and paroxetine), and CBT using prolonged exposure (PE). In PE, the patient imagines the traumatic event out loud to reduce anxiety related to talking about it, and then is exposed to the places or things that trigger distressing thoughts or feelings. For SAD, the approved medication treatments are SSRIs (sertraline and paroxetine, including paroxetine CR), while group CBT with exposure therapy is the best psychosocial intervention (9). For specific phobias, the optimal treatment is CBT and exposure therapy. For all anxiety disorder, anxiolytic agents such as benzodiazepines can be used as a temporary adjunct to aid in minimizing anxiety, in particular when starting a medication therapy. In general, it is important to try to avoid long-term use of benzodiazepines for anxiety disorders, since it may lead to tolerance and increase risk of abuse or dependence, although particularly resistant cases may require longer-term administration.

The past decade has witnessed a rapid growth in our knowledge of the neurobiological basis of anxiety, through our examination of the behavioral components of the fear response. Significant advances in the spatial and temporal resolution of brain imaging techniques have clarified the neuroanatomical pathways responsible for processes relevant to fear and anxiety in humans, such as fear conditioning, acquisition, consolidation and reconsolidation, and extinction (see Table 1 for a glossary of terms). Animal studies, primarily on rodents, have shown that the amygdala, in connection with a complex network including the prefrontal cortex (PFC), thalamus and hippocampus, is integral to multiple aspects of emotional processing, including mediating adaptive and pathological fear responses (10). Neural circuits, defined by brain imaging and the use of pharmacological challenge studies, have yielded clues about receptor and gene expression that may elucidate the potential causes and vulnerabilities to anxiety disorders.

This article will review research relating to the basic mechanisms of the neurobiology of fear and the application of this research to anxiety disorders (in particular specific phobias, SAD, PD and PTSD), and will suggest potential therapeutic strategies for the future. As many of the initial pharmacological findings derived from animal models are now being applied to patients in the anxiety clinic, there is an emergence of a new translational field in psychiatry.

Classical Fear Conditioning

The original model of classical conditioning was most famously demonstrated by Ivan Pavlov (11). It begins with the observation that certain stimuli, referred to as unconditioned stimuli (US), reliably yield an unconditioned response (UR). When a neutral stimulus is paired with the US it may also yield the same response through conditioning. Under these conditions the neutral stimu-

TABLE 1
Terms Used in Conditioning

Term	Definition
Classical Conditioning	A process by which previously neutral stimuli acquire meaning to the organism.
Unconditioned Stimulus (US)	A trigger that produces an automatic, unlearned response.
Unconditioned Response (UR)	A naturally occurring reaction to an US.
Conditioned Stimulus (CS)	A neutral trigger that, through classical conditioning, is able to produce a conditioned response.
Conditioned Response (CR)	The learned reaction to a CS.
Generalization	The ability to respond similarly to stimuli which are qualitatively different but functionally equivalent.
Acquisition	The initial stage of learning, where a neutral stimulus (CS) is associated with a meaningful stimulus (US) and obtains the capacity to elicit a similar response (CR).
Short-term memory	Memory of a limited amount of material that is held for a short period of time.
Long-term memory	Memory with a very high capacity which lasts over a long period of time.
Consolidation	The process by which short-term memory is converted into long-term memory.
Retrieval	Locating and returning to consciousness information stored in long-term memory.
Reconsolidation	A process by which a previously consolidated memory, which has been retrieved and becomes labile, undergoes another consolidation.
Extinction	The process by which a CS loses the ability to elicit a CR.

lus is referred to as the conditioned stimulus and the response to the CS is the conditioned response (CR). Pavlov's experiment involved a dog that was presented with food (US) and salivated (UR). Then, the tester presented the food while at the same time ringing a bell (a neutral stimulus), and repeated the pairing several times. Finally, the food was taken away and the tester again rang the bell (CS), which produced salivation (CR).

Pavlovian fear conditioning occurs when a neutral stimulus is paired with an aversive stimulus. For instance, in the Little Albert experiments (12), an 11-month-old boy was given a rat (CS) to play with, and showed no fear response. Then, when again presented with the rat and simultaneously a very loud noise (US), Albert began to cry (UR). With repeated pairing of the rat and loud noise, Albert was shown the rat alone (CS) and began crying (CR). Even stimuli similar to a rat (any small, white, furry object) would create a fear response in the boy. Although fear responses serve an evolutionary valuable function in protection from potential dangers, they may also be maladaptive in that any contextual stimulus can become associated with recurrent fear and anxiety (i.e., generalization). In typical fear-conditioning rodent models, a US such as a mild electric footshock is used to elicit a CR, like behavioral freezing or alterations in blood pressure or heart rate.

Neuroanatomy of Anxiety

The area of the brain responsible for the acquisition and expression of fear conditioning is the amygdala (13). Located within the medial temporal lobe, the amygdala is comprised of 13 nuclei, three of which, the basal amygdala (BA), lateral amygdala (LA), and central nuclei, are involved in the pathways of fear response (14). Stimuli received by the sensory thalamus are transmitted to the LA, and then are transferred to the central nucleus (CA) ("short loop" pathway). The BA also serves as a connection between the LA and central nucleus. The "long loop" pathway sends signals to the LA from the sensory cortex, insula, and prefrontal cortex (15, 66; Figure). From there, the information projects to the effector sites in the brain stem and hypothalamus, which produce the autonomic and behavioral manifestations of the acute fear response (16). It has been shown that the LA is the area responsible for memory consolidation and plasticity in fear conditioning (17, 18). Disruption or lesions of the LA or CA can disrupt the acquisition of conditioned fear and long-term contextual fear memory (19–21); there is evidence that lesions of the BA can affect fear responses (22). The molecular mechanism by which fear acquisition occurs in the LA is long-term potentiation (LTP) (23). It is proposed that consolidation of memory occurs during a process in which calcium enters the cell via *N*-methyl-*D*-aspartate (NMDA) receptors and through

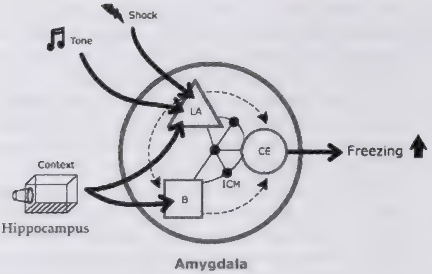

Figure. Fear conditioning circuitry.

In auditory fear conditioning, animals learn to fear an innocuous tone. By pairing tone and shock, the tone acquires the capacity to elicit defensive reactions, such as freezing (arrow pointing up). Tone and shock stimuli converge in the lateral amygdala (LA), resulting in associative plasticity in the tone—LA pathway. Subsequent presentations of the tone can now activate LA neurons. The LA then communicates with the central nucleus (CE), which controls the expression of fear by way of connections to specific circuits that mediate freezing behavior. The LA connects with CE directly and by way of connections to other amygdala areas, including the intercalated cell masses (ICM), which gate the output, and the basal nucleus (B), which processes contextual information from the hippocampus.

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voltage-gated calcium channels (VGCCs) (24). Blockage of the VGCCs will disrupt short-term memory but not long-term memory, indicating that this pathway requires only NMDA receptors to be active (25–27). Some animal studies have shown that blockage of NMDA receptor by the antagonist D,L-2-amino-5-phosphonovaleric acid (APV, AP5), will block fear acquisition, but not expression (28–30), although more recently studies have shown that both processes are inhibited (31–33). Gene studies have shown high expression of NMDA receptors in the hippocampus as well, indicating the importance of this brain structure in Pavlovian conditioning (34). As in the amygdala, blockage of these receptors will inhibit conditioned fear responses (35, 36).

The application of these preclinical findings to humans is, currently, limited, but potential avenues include the use of NMDA receptor antagonists and calcium channel blockers to impair memory consolidation and thereby treat anxiety symptoms. Memantine, a non-competitive NMDA receptor antagonist, is widely used as a memory-enhancing agent in patients with moderate-to-severe Alzheimer's disease, most likely by improving neuronal plasticity and reducing excitotoxicity in the hippocampus (37). It has also been found to have anxiolytic properties in some animal studies (38, 39), but not in others (40, 41). It has not yet been studied as a primary anxiolytic agent in humans. Interestingly, Zarate and colleagues (42) found in a double-blind, placebo-controlled trial, that memantine was not effective in the treatment of major depressive disorder, suggesting potentially different pathways for mood modulation. Lamotrigine, a glutamate antagonist that acts by blockade of voltage-dependent sodium channels and calcium channels, is indicated for treatment of seizures and bipolar disorder. Mirza and others used a conditioned emotional response (CER) model in rats, with the pairing of houselight (CS) to electric footshock, to determine if the CS would associate with reduced lever pressing to receive food. One of their findings was that a Na^+ agonist blocked the anxiolytic effects of lamotrigine, while a Ca^{2+} channel agonist did not, suggesting that the anxiolytic properties may be mediated by blockade of sodium channels (43). Hertzberg and colleagues used lamotrigine in a small double-blind trial of patients with PTSD, and found it to be more efficacious than placebo in reducing the severity of symptoms of PTSD, including re-experience and avoidance (44). VGCC inhibitors provide another potential avenue for treatment of anxiety disorders (see Table 1). For example, pregabalin, an anticonvulsant that binds to the alpha-2-delta protein to block VGCC, has shown promise as a therapeutic agent for generalized anxiety disorder (GAD) (45), and might gain FDA approval by the end of 2007.

Consolidation and Reconsolidation

The conversion of labile, short-term memory into long-term memory is called consolidation, in a process dependent on protein synthesis (46, 47). While originally thought to occur once, the process in which transient information is permanently stored may require new protein synthesis after retrieval (48, 49). The memory trace, upon retrieval, is unstable and is required to undergo reconsolidation before it can be restored (50). Typically, memories are not stored individually, but instead as associated complexes, in which all related components are stored together (51). Recently, Debiec and colleagues (52) used a second-order fear conditioning (SOFC) paradigm, meaning that one CS was linked to another CS to cause an US (53), to test whether a blockade of protein synthesis would disrupt one memory, or the entire associative network. They showed that only directly reactivated memories become labile, but that indirectly reactivated memories within the association complex are not affected (54). These findings may play a role in understanding how stressful events can be unlearned, without causing amnesia for memories temporally associated with the conditioned fear stimulus.

Reconsolidation offers a model for anxiety as a fear response in the absence of a US. It occurs via repeated activation of a memory, which enhances its retention (55). It is well established that emotionally laden stimuli, when compared to neutral stimuli, are more likely to be recalled, and are likely to cause amnesia for words preceding it (56).

Reconsolidation requires involvement of NMDA receptors and beta-adrenergic receptors, with induction by the cyclic adenosine monophosphate response element binding protein (CREB) (54). Propranolol, a central-acting, beta-adrenergic receptor antagonist, has been consistently shown to block recognition and recall of emotionally laden words and memories (57–61), while preserving neutral words. The drug also acts to restore the amnesia caused by the emotional stimulus. Furthermore, propranolol acts to block reconsolidation only and does not interfere with integration of new memories (62). These findings have led researchers to test beta blockers in humans with traumatic experiences, in one case investigating the effects on recall of distressing memories (63). Pitman and colleagues conducted the only randomized controlled trial of propranolol in acute trauma victims, who were administered the medication or placebo within 6 hours of exposure to trauma and continued for 10 days (64). Although they found less severe symptoms of PTSD, as measured on the Clinician-Administered PTSD Scale (CAPS), in those receiving propranolol vs. placebo at 1 and 3 months (with three months being the point where PTSD can first be diagnosed), the results were not statistically significant. With improved study design and larger sample size, further studies are underway to test the efficacy of beta-adrenergic receptors in the prevention of PTSD.

Extinction

In Pavlov's experiment of classical conditioning, the dog ceased to salivate when the bell was rung (CS) but no food was presented (US) (11). This phenomenon is known as extinction. It does not involve, as the name implies, erasure of old information, but rather it is caused by the integration of new memory (65). The amygdala plays a key role in fear extinction, as do the medial prefrontal cortex (mPFC) and hippocampus. The LA is responsible for decreased firing with continued presentation of the CS, while the mPFC inhibits firing of amygdala neurons, under the modulation of the hippocampus (66). It is the mPFC that is thought to regulate extinction of long-term memory (67). This has been supported by studies showing blocking of extinction after lesion of the mPFC (68), and by blockade of protein synthesis in the mPFC (69). Exposure to chronic stress can also affect the mPFC's ability to modulate extinction, via retraction of dendrites (70, 71). Miracle and colleagues showed that rats exposed to restraint stress showed reduction in extinction 24 hours after initial extinction (72).

Much like in fear acquisition, an important component of extinction is activation of glutamatergic NMDA receptors in the amygdala. It has been shown that NMDA receptor antagonists, like AP5, can cause blockade of extinction, as measured by startle response (73). Conversely, partial NMDA agonists, such as *D*-cycloserine (DCS), have been shown to facilitate extinction. Walker and others used systemic administration, and direct amygdalar infusion, of DCS into rats, and found a decrease in fear-potentiated startle to CS compared to control animals (74). Ledgerwood's group confirmed these findings, and also determined that DCS not only aided in extinction of the original CS, but also reduced but didn't extinguish fear response to a CS paired with another CS, (75). This suggests that DCS may have an effect on extinction of generalized fearful stimuli, such as all furry objects, which caused crying in Little Albert (see above).

Investigation of the use of DCS in humans with anxiety disorders is already underway. Since DCS acts only to enhance extinction to fear responses, and is not a direct anxiolytic, it is used with exposure therapy or CBT to show an effect. This was evidenced by one small study that used DCS in PTSD patients with limited effect, but did not employ concomitant psychotherapy (76). Ressler and colleagues used 2 single-dose administrations of DCS 2–4 hours prior to exposure therapy in patients with phobic avoidance of heights, and found marked reductions in fear and avoidance symptoms that persisted for 3 months after treatment (77). A recent trial used DCS to augment group exposure therapy in patients with social anxiety disorder, and found rapid improvement in symptoms in patients compared to controls, who received exposure therapy and pill placebo (78). In summary, DCS has shown promise an adjunct treatment for patients with anxiety disorder by enhancing the learning associated with the treatment.

The inability of a person to extinguish a maladaptive fear response to a CS, due to a disruption in the process of extinction, can result in persistent anxiety. Two pathways for the treatment of anxiety presented so far are the disruption of consolidation of emotional or traumatic memories (see above), and facilitation of the extinguishing of aversive stimuli. The second area is under intense investigation. In addition to using DCS, there are other potential agents being used in animal studies to aid in enhancing extinction. These include yohimbine, an alpha-2-adrenoreceptor antagonist (79), L-type VGCC agonists (27, 80), cannabinoid receptor 1 agonists (81, 82), and mu-opioid receptor blockers (Table 2; 83, 84). Investigation of the applicability of these mechanisms to humans is warranted.

Conclusion

Using Pavlovian conditioning as a model, the pathophysiology of the fear response has been clarified over the past several years. Many animal studies have shown how these learning paradigms can be applied to humans, and how they can be used to understand the causes of anxiety. Imaging studies, using functional magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning, have helped trace and pinpoint the areas of the brain responsible for induction, maintenance, and unlearning of fear. Although the amygdala and prefrontal cortex are the primary sites of fear acquisition and extinction, other areas are being shown to play important roles as well. In addition, there are neurochemical pathways, not well understood, that may be proven to play a role in anxiety disorders.

The DSM-IV currently categorizes the anxiety disorders by clinical signs and symptoms. The Committee of the DSM-V Prelude Project, is considering re-classifying the anxiety disorders by several hypothetical approaches, including by etiology (vulnerability genes and gene/environment interactions) or by pathophysiology (neural pathways that give rise to certain symptoms) (85). This may be sensible, given the high comorbidity between mood and anxiety disorders. Using deficits in neural cir-

TABLE 2

Experimental Therapeutics for Anxiety Disorders

Therapeutic Aim: Acceleration of extinction of pathological fear responses

Clinical Application: Adjunct to cognitive behavioral therapy for specific phobias, social anxiety, and/or PTSD

Preclinical Rationale	Neurobiological Mechanism	Drug Target	Prototypic Drug	References
pharmacologic or genetic disruption of eCB neurotransmission in rodents decreases fear extinction but not memory acquisition	eCBs depress inhibitory networks involved in aversive learning	CB1 (eCB) receptor	AM404, an inhibitor of eCB break-down and reuptake	81, 82
yohimbine facilitates extinction of cue and contextual fear in mice	NE enhances the learning of fear extinction	α_2-adrenergic receptor	yohimbine	79
D-cycloserine infusion into amygdala strengthens extinction of fear-potentiated startle in rats	long-term retention of extinction requires activation of NMDA glutamate receptors in amygdala	glycine modulatory site of NMDA receptor	D-cycloserine	77, 78
in the vlPAG of rats, blockade of μ opioid receptors retards fear extinction, while inhibition of enkephalin degradation enhances it	activation of vlPAG μ opioid receptors contributes to extinction of conditioned fear	μ opioid receptors in vlPAG	RB101(S), inhibitor of enkephalin-catabolizing enzymes	83, 84
the LVGCC inhibitors nifedipine and nimodipine impair fear extinction in mice but not acquisition or expression of conditioned fear	LVGCCs are essential for fear extinction	LVGCC	L-type calcium channel agonists	27, 80

PTSD = post-traumatic stress disorder, eCB = endocannabinoid; KO = knockout; LTP = long-term potentiation; LVGCC = L-type voltage gated calcium channel; Nac = nucleus accumbens; NE = norepinephrine; vlPAG = ventrolateral quadrant of periaqueductal gray; NMDA = *N*=methyl-D-aspartate.

cuits as a means of categorization, certain disorders marked by amygdala-centric fear pathways (such as PD, PTSD, phobias) will be grouped together, while GAD may be re-classified as a mood disorder.

While unable to cover all topics related to the neurobiology of fear and anxiety, our report reviewed the pertinent findings in the area of fear conditioning, including acquisition, reconsolidation, and extinction. Finally, through investigation of these pathways and neuropeptide systems, novel therapeutic interventions can be found for a wide range of anxiety disorders, such as generalized anxiety, panic, phobias, and PTSD.

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Developmental Endocrine Influences on Gender Identity:

Implications for Management of Disorders of Sex Development

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Abstract

When a baby is born, the first medical pronouncement is usually, "It's a boy," or "It's a girl." In most cases, this pronouncement is based simply upon the appearance of the child's external genitalia. Due to variations in the process of sexual differentiation, sometimes the gender that should be assigned is not apparent from inspection of the external genitalia, either because they are "ambiguous" or because their appearance is not congruent with the internal anatomy. Decisions must be made not only about the most appropriate gender to assign the infant but also about the medical and rearing practices that will facilitate optimal psychological development and quality of life for the affected individual. This article will review the approach to managing gender disorders that has evolved since the 1950s. Three issues are identified as central to current shifts that are occurring in the management of these disorders: (a) increased understanding of the biological substrates of gender identity; (b) questions regarding the indications for irreversible cosmetic genital surgeries as a means of reinforcing gender assignments in infancy, and (c) ethical issues pertaining to informed consent and who is entitled to give it, particularly with regard to surgical gender reassignments in infancy. In keeping with the neuropsychiatry theme of this issue, the focus of this article is on prenatal sexual differentiation of the brain as it pertains to the question of psychosexual neutrality at birth.

Key Words: Intersex, sexual differentiation, sex assignment, gender assignment.

Introduction

PARTICULAR TERMS may be defined differently by various authors, so it may be helpful to begin by defining those terms as they will be used here. *Sex* will be used to refer to the biological variables that can be described as either male or female (e.g., genes, chromosomes, gonads, internal and external genital structures), while *gender* will refer to social categories (e.g., man or woman, boy or girl) or factors related to living in the social role of a man or a woman. *Gender identity* refers to one's sense of belonging to the male or female gender category (1), while *gender role* refers to behaviors (mannerisms, style of dress, activities etc.) that convey to others one's membership in one of those categories (1). *Sexual orientation* refers to one's pattern of erotic responsiveness and will be described here as *androphilic* (attracted to men), *gynephilic* (attracted to women), or *bisexual* (attracted to both).

The course of normative development culminates in full concordance among all of the biological variables of sex (i.e., either all male or all female). In *intersex* disorders, however, one or more of those variables is discordant with the others or its differentiation is intermediate between male and female norms. *Intersex* became the preferred term to encompass a variety of syndromes previously classified on the basis of gonadal histology as *true hermaphroditism* in which both testicular and ovarian tissue are present in a single individual, and *pseudohermaphroditism* in which only one type of gonadal tissue is present. Due to disagreements as to whether or not particular disorders should be considered intersexed (2), the term *disorder of sex development* is gaining currency to refer to any congenital condition in which development of chromosomal, gonadal or anatomical sex is atypical (3). It has been estimated that a child is born with external genitalia so noticeably atypical that a specialist in sexual differentiation is consulted about once in every 1,500–2,000 births. This article deals primarily with that population, whether or not all meet a particular authority's definition of intersex. For discussion of the definitions and frequency of intersex, the reader is referred elsewhere (2, 4, 5).

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Beginning in the 1950s, John Money and colleagues (6) observed that because intersexes are neither completely male nor completely female they "are likely to grow up with contradictions existing between the sex of assignment and rearing, on the one hand, and various physical sexual variables, singly or in combination." They collected data on the psychosexual development of children born with various intersex conditions in order to determine whether their gender role and identity were more likely to be concordant with the sex of assignment and rearing, or with one or another of the physical variables of sex. Of 105 intersexes studied, only 5 had a gender role or identity that was "ambiguous and deviant from the sex of assignment and rearing." Thus, they concluded, along with Ellis (7), that the sex of assignment and rearing is a much better predictor of gender role and identity than the biological variables of sex.

This evidence for the early malleability of gender identity instigated a shift away from prior attempts to assign gender to intersexed individuals on the basis of gonadal histology or chromosomal analysis. Instead an "optimal gender policy for psychosocial and medical management" of intersex conditions was developed (8, 9), aimed at optimizing their prognosis with respect to six variables: reproductive potential, sexual function, minimization of medical procedures, gender-appropriate appearance, stable gender identity and psychological well-being. Although it was appreciated at that time that intrauterine hormones might exert sexually differentiating effects on the fetal brain, it was widely accepted that the effects of nurture outweigh those of nature with respect to psychosexual development. Prompt surgical normalization of external genital anomalies was, therefore, viewed as necessary to establish the dominance of nurture over nature. More specifically, external morphology congruent with the assigned gender was viewed as essential both to convince the affected child that he/she was truly a member of the assigned gender and to convince the parents who were responsible for unambiguously rearing the child as a member of the assigned gender (8). Compared to phalloplasty, vaginoplasty provides better cosmetic and functional results, and a small penis was believed to be a tremendous psychosocial burden for a boy (8, 10). Thus, due to the belief in the early malleability of gender, a majority of intersexed infants with an absent or small phallus were assigned as female regardless of the status the other biological variables of sex. Even male infants who were not intersexed but who had a stretched phallus length of less than 2 cm were sometimes reassigned as female (10).

Over the past half century, a variety of lines of converging evidence—including follow-up studies of intersexed individuals and non-intersexed individuals whose gender was surgically reassigned in infancy—suggests that the organizing effects of prenatal endocrine factors on the subsequent emergence of gender identity is much stronger than previously thought (11–13). Consequently, the management of intersex disorders, particularly the initial gender assignment, is increasingly taking into account exposure to these factors. Moreover, the practice of performing cosmetic genital surgeries on infants to reinforce gender assignments is currently being challenged on a variety of medical and ethical grounds including the fact that these surgeries generally cannot be reversed if the affected individual subsequently rejects the assigned gender (14–17). This article will begin by reviewing the neurobiology of gender identity with an emphasis on the role of prenatal endocrine factors, and will conclude by considering this information in the broader context of shifts that are taking place in the management of intersex and other disorders of sex development.

Neurobiology and Gender Identity

Overview of Sexual Differentiation

Hormonal contributions to sexual differentiation of the brain have been extensively reviewed recently elsewhere (18, 19). Animal studies have contributed substantially to the formulation of a prenatal hormonal hypothesis for both sexual orientation and gender identity. The prenatal hormonal hypothesis draws largely on the observation that the balance between male and female copulatory and other reproductive behaviors in animals is strongly influenced by the magnitude and timing of early androgen exposure. In addition, anatomical sex differences in regions of the rodent brain implicated in the regulation of these behaviors have been found to have a similar developmental hormonal dependence. The best studied of these neuroanatomical sex differences, the sexually dimorphic nucleus of the preoptic area (SDN-POA) in rats appears to have a homologue in the primate (20) and human (12, 21, 22) hypothalamus. The human nucleus, known as the third interstitial nucleus of the anterior hypothalamus (INHA3), is larger in males than in females (12, 21, 22). It has been reported to vary with sexual orientation such that it is larger in gynephilic compared to androphilic individuals (12). In addition, the size of a portion of the bed nucleus of the stria terminalis has been reported to be sexually dimorphic in rats and humans, and to vary in humans as a function of gender identity but not sexual orientation (13, 23). Specifically, the nucleus was reported to be larger in individuals with a male as opposed to a female gender identity, regardless of their genetic, gonadal or hormonal status and regardless of the direction of their sexual orientation (13, 23). These human studies must be viewed tentatively pending corroboration, and, to date, there have been no empirical investigations into the prenatal hormonal dependence of the putative hypothalamic dimorphisms in humans.

The mammalian embryo is initially sexually bipotential (19). In the course of normal male differentiation a testis-determining gene, SRY, which is normally on the Y chromosome directs the development of testes. Subsequently, testicular secretions orchestrate the differentiation of the male genitalia and brain. Müllerian inhibitory substance, a nonsteroidal testicular secretion, induces regression of female internal genital structures, while the 5α-reduced metabolite of testosterone, 5α-dihydrotestosterone (DHT), is required for the development of male internal genital structures and for the differentiation of male external genitalia. Activation of androgen receptors by testosterone itself or by DHT appears to contribute to the masculinization of brain structure and function in some species (24). In laboratory rodents the conversion of testosterone to estrogen by aromatase enzymes within the brain plays a greater role, although the activation of both androgen and estrogen receptors may be required for full masculinization (24, 25). Not only do males and females have different hormonal requirements, but animal studies suggest that the various aspects of somatic and brain sexual differentiation occur during differing periods of development in a sequence of temporally overlapping steps (24, 26). Thus, various parameters hypothesized to reflect sexual differentiation of the brain (e.g., gender identity and sexual orientation) could vary independently from one another and from genital morphology. In the absence of the cascade set in motion by the testis-determining gene, female development ensues, at least to a first approximation.

Human testes begin to secrete androgens by the seventh or eighth week of gestation (27), a process that is initially regulated by human chorionic gonadotropin secreted by the placenta (28). By the fifteenth week of gestation, the regulation of androgen secretion is taken over by gonadotropin from the fetal pituitary, which is in turn regulated by the fetal hypothalamus. Gonadotropin secretion decreases toward the end of gestation. Thus, fetal androgen in males is elevated between weeks 8 – 24 of gestation, with peak levels occurring between weeks 14 – 16 (29). In males, the level of testosterone increases from birth to a peak at 1 – 3 months and then decreases to prepubertal levels by 4 – 6 months (30). The ovary is relatively quiescent prenatally but secretes substantial levels of estradiol during the first 6 – 12 months after birth. A sharp reduction of gonadal activity then occurs in both sexes until 10 or 12 years of age, when sex-characteristic adult hormonal profiles emerge (19). Thus, hormonal influences could conceivably influence psychosexual differentiation prenatally (8 – 24 weeks of gestation), during the first 6 – 12 months postnatally, and again at puberty.

Human Studies Relevant to Biology and Gender Identity

Clinical data spanning more than half a century, relevant to the question of early hormonal influences on gender identity, have been reviewed extensively by Zucker (8). The following is a summary and update of that review, with an emphasis on cases that were followed at least into late adolescence and in which an assessment of gender identity and role were documented. The syndromes are grouped into those in which the developing brain was exposed to either a full or a partial complement of masculinizing influences. This division is based on the hypothesis that the likelihood of problems with the acceptance of a female gender assignment is related to the degree of early brain masculinization. Various syndromes will be described first, with their implications regarding gender differentiation discussed at the end of this section. For discussion of disorders of sex development not reviewed below, the reader is referred elsewhere (3, 31 – 33).

Syndromes with a Normal Complement of Masculinizing Hormonal Influences Prenatally

Ablatio penis does not refer to a disorder of sex development but instead refers to the accidental or traumatic loss of the penis in infancy in otherwise normal males. Four cases reassigned to the female gender prior to 2 years of age have been reported (8). Of these, at least 2 had switched to a male gender identity by or during puberty, while 2 had retained a female identity at last follow-up (ages 17 and mid-20s). Detailed information is available for only two of these cases. The first detailed case was first described by Money and Ehrhardt (1) and has been widely publicized as the case of John/Joan. This case will be discussed in some detail because of the inordinate impact it has had on the field.

One of a pair of normal monozygotic 46XY twins suffered accidental penile ablation at the age of seven months. A decision for gender reassignment was made at 17 months, with orchiectomy and preliminary vaginoplasty occurring at 21 months (1, 8, 31). Follow-up at seven years suggested that the patient had accepted the female gender identity and that the twin brother was a normal male (1). Two years later, the patient was described as having tomboyish traits but that "Her activity is so normally that of an active little girl...." (34). It was concluded that "...gender identity is sufficiently incompletely differentiated at birth as to permit successful assignment of a genetic male as a girl...." (34). Over the next two decades that conclusion was cited in innumerable medical review articles and textbooks, and formed the crux of theories concerning the malleability of gender and surgical gender reassignment in intersexes (35). Follow-up when the patient was in his early 30s, however, revealed that he had rejected the female identity, resisted feminizing estrogen therapy, and had begun to live as a male by the age of 14. At that time he received a mastectomy and began testosterone replacement therapy and surgical procedures for phallus reconstruction (11, 35). He married a woman at age 25 and adopted her children. His suicide in 2004 has been attributed by some to the contribution of gender reassignment and its aftermath to his anguished history (36).

In the second detailed case, the patient's penis was destroyed during an electrocautery circumcision at 2 months (37) and surgical reassignment was begun at 7 months. At 26, she was reported to be confident of her female gender. Although she was sexually active with a man, she reported primarily gynephilic fantasies and described her sexual orientation as bisexual.

Cloacal exstrophy, a disorder of embryogenesis involving the genitourinary and intestinal tracts, affects both genetic males and females. Its incidence is believed to be less than one in 400,000 births. In genetic males, the external genitalia are often grossly anomalous or absent; however, testicular function is generally believed to be normal (38, 39). Genetic males with this disorder are often reassigned as female, castrated to prevent emergence of masculine secondary sexual characteristics, and treated with estrogen at puberty to stimulate the development of female secondary sexual characteristics. No detailed post-pubertal follow-up studies have been published on reassigned individuals. In one case report, an affected male reared as female from birth lived as a woman for 52 years. Then, upon the death of her parents, she underwent reconstruction as a man. In a series of 10 affected 46XY individuals between the ages of 4 and 14 who were castrated and unequivocally raised as girls from birth, all were close to the male range in attitudes, activities and behaviors (38). Three had declared themselves to be male (at ages 8, 9, and 12 years, respectively). In a detailed clinical study of affected adolescents who were reared as males, all were described as exhibiting psychosexual dysfunction and anxiety leading to social and sexual developmental impairment (40). Nevertheless, all retained a male gender identity.

Penile agenesis is a condition in which the penis fails to differentiate, although the scrotum is normal and contains normally functioning testes (41). No hormonal abnormality of prenatal onset has been reported in patients with this rare disorder of mixed etiology. Although more than 20 cases have been reported (8), post-pubertal follow-up with assessment of gender identity is available for only a few. Of 4 assigned males, all had retained a male identity at last follow-up, at ages 13, 15, 22 and 45, respectively. Of more than a dozen assigned and reared as females, post-pubertal assessment is available for only two. Of those, one was reported to be content with her female assignment at age 13. The other identified as female at age 15 but was living as a man at age 27.

Syndromes with an Incomplete Complement of Masculinizing Influences

Congenital adrenal hyperplasia, which occurs approximately once in 13,000 births (4), involves an enzymatic abnormality in cortisol synthesis that results in an overproduction of androgens beginning during the fetal period (42). In genetic males, no genital abnormality ensues; however, in genetic females varying degrees of external genital masculinization occur ranging from mild clitoral enlargement to complete fusion of the labioscrotal folds with a phallic urethra (43). There is at times uncertainty regarding gender assignment at birth. Cortisol replacement therapy can minimize further virilization after birth and allow normal ovarian function and fertility to emerge with puberty. In one large cohort 9% of genetic females were assigned and reared as males without reported complications (42). As early detection increases due to state-mandated neonatal screening, the proportion assigned as male is likely to decrease in keeping with the optimal gender policy, which places emphasis on female reproductive potential.

Affected individuals who were reared as females have been studied extensively with regard to cognitive profiles (44), childhood gender conformity (45), gender identity (46), and sexual orientation (47). The vast majority of affected individuals retain their female gender identity into adulthood although with a statistically increased incidence of gender nonconformity (45, 46), gender dysphoria (48) or ambivalence about gender (49) in childhood and gynephilia in adulthood (46, 47). Four cases, however, have been described in which a male identity emerged gradually between late adolescence and adulthood despite having been assigned as female within a few weeks of birth (50). Gender dysphoric subjects appear to be less willing to participate in follow-up studies compared to subjects without gender dysphoria (8). The proportion of affected individuals who change from female to male gender identity is difficult to know with any degree of certainty; however, various authors have estimated that proportion to be as low as 2% and no higher than 10% (3, 8). Both estimates are much higher than the rate (approximately 1 per 34,000) of transsexuality among normal females (8).

Complete androgen insensitivity is believed to have a minimal incidence of one per 99,000 births but may be as high as one per 13,000 (4). In this condition 46XY individuals develop normally functioning testes but lack functional androgen receptors (24). They develop normal female external genitalia because their tissues are unable to respond to androgens. They are capable of responding to Müllerian inhibitory substance, however, so their internal female genital structures regress. Untreated, they develop breasts and female-typical fat distribution at puberty in response to estrogens derived from testosterone synthesized by their testes. Historically, these individuals were assumed to be normal females at birth and did not come to medical attention until testes descended into the labia, or until they failed to menstruate or conceive children. The published literature does not contain any reports of affected individuals changing to a male gender identity (9). Thus, in the absence of functional androgen receptors, female gender identity appears to be the rule in individuals with an XY karyotype and normally functioning testes. While it has been suggested that in the absence of functioning androgen receptors, these individuals would have female-typical brain differentiation (19), in laboratory rodents androgens appear to orchestrate differentiation of the male brain primarily by interaction with estrogen receptors after conversion to estrogen by aromatase enzymes in the brain (24). It has, therefore, been suggested that humans, in contrast to rodents, require functional androgen receptors for male brain development (24).

Partial androgen insensitivity refers to disorders in which there is a partial resistance to androgens, which results in external genitalia that are only partially masculinized. No reliable statistics are available for the frequency of this disorder, which is generally believed to occur with a lower incidence, perhaps one tenth that of complete androgen insensitivity (4). The degree of external genital masculinization varies with the degree of androgen resistance, leading to considerable phenotypic variation and overlap in appearance with other syndromes. Affected individuals have been assigned and reared as either males or females depending in part on the degree of external genital virilization. In one series of 6 individuals assigned as female (8), 5 retained the female gender identity into adulthood. Following a long history of masculine gender role interests and gynephilia, the sixth requested gender reassignment at age 30. Another report describes 10 affected individuals of whom eight were reared as boys, one as a "hermaphroditic girl" and one as a girl (51). At follow-up between 13 – 39 years it was concluded that gender identity differentiated in accordance with the gender of rearing. A third report describes 8 patients, 7 of whom were assigned as female at birth (48) and followed up between the ages of 6 – 23. Details on gender identity were not given; however, the authors concluded that the female assignment had been wrong on the basis of the patients' "boyish behavior.... In particular, the wild, rough play ... [which was] difficult for their parents to regulate."

5α-reductase deficiency affects 46XY individuals. During fetal development the gonads differentiate into normal testes and secrete appropriate amounts of testosterone; however, due to the deficiency of 5?-reductase, affected individuals are unable to convert testosterone to dihydrotestosterone in amounts sufficient for the external genitalia to masculinize normally. Consequently the newborn may have a phallus that more closely resembles a clitoris than a penis, and unfused labioscrotal folds resembling labia majora. In the absence of sophisticated diagnostic testing, affected individuals have often been assumed to be females at birth and have been reared accordingly (52, 53). At puberty, however, testosterone and not dihydrotestosterone is the essential androgen for growth of the male external genitalia and the emergence of male secondary sex characteristics (54). Thus, a masculinizing puberty ensues: the phallus markedly enlarges, the testes descend into the labioscrotal folds, the beard grows, the voice deepens and a masculine habitus develops (52, 53).

The prevalence of this disorder in the general population is unknown (4). It has been studied extensively in the village of Las Salinas, Dominican Republic, where its prevalence is unusually high due to consanguineous marriages (52, 53). Of 18 individuals who reportedly had been assigned and reared as females from birth, 17 changed to a male gender identity and 16 to a male gender role at puberty. The authors suggested that male gender identity and gynephilia "appear to be testosterone and not dihydrotestosterone related...and that sex of rearing as females...appears to have a lesser role than the presence of two masculinizing events—testosterone exposure *in utero* and again at puberty with the development of a male phenotype." Because the studied individuals came from inter-related families living in the same village, questions have been raised about the possibility of ambiguities in the gender socialization of many of the affected individuals (53, 55). Similar accounts of gender change from female to male have been made in cohorts from Mexico, Papua New Guinea and Brazil (8, 54, 56).

17β-hydroxysteroid dehydrogenase deficiency usually results from a missense mutation (54) and occurs with unknown frequency. The mutation results in a deficiency of the enzyme that catalyzes the terminal step in testosterone synthesis. Affected 46XY infants are born with female external genitalia despite the presence of testes and male internal structures (54). The deficit in testosterone produces a corresponding deficit in its androgenic and estrogenic metabolites believed to play a role in masculinization of the brain. The deficiency usually becomes less severe with time and many affected individuals eventually have male-typical testosterone levels. They are usually assigned as female at birth and come to medical attention because of virilization at puberty or a failure to menstruate. Between 40% and 50% of affected individuals, even one who made essentially no hydroxysteroid dehydrogenase (17β-HSD) (54), have been reported to switch from a female to male identity postpubertally.

Micropenis is a condition in which penile length is at or below the 10th percentile for age-graded norms (8). Androgens are necessary at two points in fetal development for a normal penis to form: early in fetal life to sculpt the bipotential genital precursor into a penis and scrotum and subsequently in fetal life to enlarge the penis. Micropenis is believed to occur in XY individuals if androgen levels are insufficient for the penile growth after the initial masculinization of the external genitalia has already occurred. Of 16 reported cases who were assigned and reared female, follow-up is available only for 8 (ages 10–25), all of whom were described as having appeared to have developed a female identity, although a detailed history was obtained from only one adult subject (8). In contrast, adulthood follow-up is available for 22 affected individuals who were assigned and reared as males (8). Of these, all were judged to have retained a male gender identity. One, however, expressed feelings of inferiority related to his small penis and reported childhood fantasies of gender reassignment. After gynephilic experimentation, he exhibited an androphilic orientation in adulthood. In one group study of 9 individuals in which all retained a male identity, childhood gender nonconformity was noted in 4, an androphilic orientation in three and gynephilic orientation in six. In a second group study of 12, all retained a male identity and a gynephilic orientation was assumed for at least nine, seven of whom were married or cohabitating with a woman.

Summary and Implications of Clinical Observations

The above review underscores the paucity of intersexed and gender reassigned cases for which detailed follow-up is available into adulthood. Moreover, it is clear that an individual may undergo a transition in gender identity while restricting the social contexts in which gender role behavior reflects that transition, and that such transitions may occur as late as middle age. The likelihood of rejecting female assignment appears to be increased in androgen-responsive individuals born with testicular tissue the longer that tissue is left in place, even prior to puberty. This could reflect the duration of reinforcement of a male identity prior to reassignment or ambivalence resulting in delays in the reassignment. Alternatively, it could reflect increased masculinization of the brain during the early postnatal surge of testosterone secretion (30). The data on individuals with 5?-reductase and 17β-HSD deficiencies suggest that the probability of switching to a male gender identity and role after female reassignment is increased further in androgen-sensitive individuals whose testes are left in place until puberty. The data do not justify the conclusion that prenatal androgen exposure produces a brain that is hardwired for male gender identity at birth. Instead, an effect of prenatal androgens may be reinforced by the elevated androgen secretion that occurs in the neonatal period and again at puberty.

Implications Regarding Hormonal Pathways Involved in Gender Differentiation

Although individuals with complete androgen insensitivity possess normal testes and all the hormones and metabolic machinery necessary to masculinize the rodent brain (i.e., testosterone, aromatase enzyme, estrogen receptors), all reported cases have been reared unambiguously as females, have retained that identity into adulthood, and have been described as having stereotypically feminine interests and behaviors as children (8). Thus, if prenatal hormones exert an organizing influence on the human brain with respect to gender, masculinization of the brain in this regard must be mediated primarily via androgen receptors. The evolution of masculine behavior and male identity among individuals with 5α-reductase deficiency suggests that those androgen receptors may be activated by testosterone in the absence of 5α- reduction. Moreover, the outcomes among individuals with 17β-HSD, and presumably very little testosterone production *in utero*, suggest that very little testosterone is required to bias gender identity in the male direction. Compared to gender identity, sexual orientation appears to be even more sensitive to androgenic influences, as evidenced by the proportion of androgenized females who develop a bisexual or gynephilic orientation while retaining a female gender identity. On the other hand, that the androgenic requirements for male gender identity and gynephilia appear to be so low detracts from the hypothesis that either androphilia or transgenderism in otherwise normatively developed XY men results from an early androgen deficiency. The variability of gender outcomes even among related intersexed individuals known to share identical genetic mutations, suggests the importance of psychological, social and cultural factors as co-mediators of gender development. The current dominance of the hormonal theory of sexual differentiation may give the impression that gonadal secretions are fully responsible for all aspects of brain sexual differentiation. Recent work, primarily in animals, however, suggests that XX and XY brain cells behave differently, in part, because of the cell-autonomous actions of X and Y genes (18). The possibility that such actions could contribute to gender identity is only now beginning to be considered. As discussed elsewhere (57), cognitive and experiential factors must also be considered.

Implications for Gender Assignment

While this review strongly suggests that biological factors contribute to gender identity, the exact nature and magnitude of their impact are uncertain. During infancy it is not possible to predict a given individual's ultimate gender identity with certainty. A small minority of individuals (i.e., transgendered individuals) who appear normatively developed at birth develop a gender identity incongruent with the known biological variables of sex. Nevertheless, development of a male identity is strongly correlated with exposure to androgenic influences in early development. Thus, it would seem imprudent to assign infants with a small or absent phallus to the female gender if they were exposed to a full complement of masculinizing influences prenatally (e.g., individuals with penile agenesis, micropenis, cloacal exstrophy). As reviewed above, male assignment of these individuals is not without complications; however, it minimizes surgery (e.g., castration to prevent masculinization at puberty) and in many cases preserves fertility (3). Similarly, preservation of fertility as males is possible for individuals with 5α-reductase deficiency and may also be possible with 17β-HSD deficiency (3). Current estimates suggest that a majority of these individuals who are reared as females, eventually live as males. Barring cultural indications to the contrary, male assignment should be the rule.

There are no known cases of 46XY individuals with complete androgen insensitivity assuming a male gender identity. These individuals, who will be infertile regardless of assignment, should always be assigned female. In order to preserve fertility, female assignment is also currently recommended by most authorities in all 46XX cases of congenital adrenal hyperplasia (3). This recommendation holds even for those cases involving extreme masculinization of the external genitalia (3) and who, according to the above review, could likely live successfully as infertile men and are at high risk of rejecting the female assignment. Guidelines for the initial gender assignment are less straightforward in other syndromes, especially those involving exposure to intermediate levels of masculinizing influences prenatally (e.g., partial androgen insensitivity, abnormalities of gonadal differentiation or function), and for whom there is no potential for fertility. In such cases, decisions must be made on an individual basis using all that is known about the child's particular disorder, how the child's disorder is likely to influence his or her gender identity, and how the family's cognitive capacity and beliefs will impact their nurturing of the child. The aim is to optimize the prognosis with respect to the endpoints identified by the optimal gender policy as described above.

Ethical Issues in Management of Disorders of Sex Development

A distinction must be made between gender assignment (a social labelling process) and the cosmetic genital surgeries that may be done in an effort to reinforce that assignment. While it is generally agreed that parents have a legal right to determine the nature of their child's medical care, some recipients of childhood surgeries have raised the complex question of whether their parents had an ethical right to consent to irreversible genital/gonadal procedures done for non-medically threatening conditions. They hold that because genitals are concealed from the public by clothing, gender assignment and social reinforcement of that assignment can be accomplished without surgery (58, 59). While atypical genitals rarely cause illness or pain, surgery and its associated scarring may cause pain, diminution of sexual pleasure, and anorgasmia as well as other complications (17). Genitoplasty frequently involves multiple procedures throughout childhood and even the best surgical efforts sometimes fail to produce acceptable functional or cosmetic results (60, 61). Furthermore, surgery is difficult or impossible to reverse and, as children or adults, individuals with disorders of sex development may reject the gender that was assigned in infancy. Some have, therefore, suggested that elective genital surgeries should not be considered until the affected individual is old enough to possess the intellectual capacity to make an informed decision (62). In appropriate cases, puberty and the development of secondary sex characteristics may be delayed medically so that a patient's decision-making is not rushed. Many believe, however, that early surgery to address genital anomalies relieves parental distress and, thereby, improves bonding between parent and child as well as the parents' ability to nurture the child (3, 50). Systematic evidence supporting this belief is critically lacking, however. To date no studies have addressed whether this important issue is better addressed by surgery as opposed to psycho-education and counseling of the parents.

Beyond the issue of who is ethically entitled to consent to procedures employed in intersex management is the issue of what constitutes informed consent. While physicians may understandably fear that particular details of their child's sexual anomalies may exacerbate parental anxiety, parents cannot make informed decisions if information is withheld from them. Informed consent requires full disclosure of relevant information, such as physical findings, karyotype and diagnosis, as well as the known potential risks and benefits of withholding or performing each intervention that may be considered. For example, early castration requires subsequent postpubertal hormone replacement therapy, which poses its own risks. These may include elevated rates of cardiovascular disease, cancers (63, 64), or osteoporosis secondary to poor compliance with hormone replacement. Some have suggested further that in order to give informed consent, parents should also be made aware of the lack of scientific agreement on theories of gender development as well as the paucity of outcome studies following particular procedures commonly employed in intersex management (14). In some cases full disclosure of the intersex status to the parents and/or affected individual has been withheld for fear that it would introduce ambiguities into the reinforcement of the assigned gender and lead to an unstable gender identity (65). Not only is age-appropriate disclosure of one's biological status a prerequisite for informed consent, it precludes the possibility that a patient will discover his or her intersex status in an uncontrolled setting in which a catastrophic psychological reaction is possible.

Conclusions

Detailed long-term follow-up and assessment of quality of life have been reported for exceedingly few individuals with disorders of sex development. More research is clearly needed to elucidate, on a syndrome-by-syndrome basis, what clinical practices are likely to yield the best quality of life in affected individuals. Three issues are central to current shifts that are occurring in the management of these disorders: (a) increased understanding of the biological substrates of gender identity; (b) the indications for cosmetic genital surgeries in the management of these disorders; and (c) ethical issues pertaining to informed consent and who is entitled to give it. In addition, a re-examination of many aspects of intersex management has been precipitated by input from advocacy groups comprising adults with disorders of sex development and the parents of intersexed children (66, 67, 68). One such group, which also includes health care providers, The Consortium on the Management of Disorders of Sex Development, has recently published clinical guidelines for health care professionals (59) and a handbook for parents (58). Among other sets of published guidelines, these uniquely reflect the input of those with the highest stake in intersex management decisions—the recipients of interventions based on those decisions.

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Psychiatric Manifestations of Nonconvulsive Status Epilepticus

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Abstract

Nonconvulsive status epilepticus (NCSE) is clinically characterized by altered mental status and the diagnosis is confirmed by electroencephalography. Absence status (AS) and complex partial status (CPS) are the two primary types of NCSE. Patients in NCSE may exhibit a wide range of clinical presentations including subtle memory deficits, bizarre behavior, psychosis, or coma. While prognosis is dependent on the underlying etiology and possibly related to duration of the event, there is limited research in this area. Treatment focuses on correcting underlying pathologic abnormalities such as hyponatremia or drug toxicity, and initiating pharmacologic therapy. The benzodiazepines are considered the first line treatment for both AS and CPS.

Key Words: Nonconvulsive status epilepticus, absence status, complex partial status.

Introduction

NONCONVULSIVE STATUS EPILEPTICUS is a term that incorporates a number of disparate conditions that have the common denominator of prolonged altered mental status due to ongoing seizure activity. Prognosis varies depending on the underlying etiology. The clinical presentation can vary from minimal confusion to bizarre behavioral manifestations to psychosis to coma. Consequently, the diagnosis can be missed and, if the entity is not considered, can at times misinterpreted to be psychiatric in origin. The recognition of this entity was made possible by the introduction of the electroencephalogram (EEG) in the 1930s, which allowed for clinical and EEG correlation. Nonetheless, to this day, it can still represent a diagnostic challenge for both the neurologist and the psychiatrist Indeed, because its primary manifestation is an alteration in behavior, NCSE serves as a model condition defining the field of neuropsychiatry.

In 2004, a prestigious group of neuroscientists met to discuss the definition, diagnosis, and management of NCSE (1). That goal was to arrive at a consensus that would facilitate communication and research in this area. Interestingly, the group did not include a psychiatrist despite the fact the a significant number of patients with NCSE are misdiagnosed as having a psychiatric condition which at times leads to a delay in receiving the appropriate management (2). The objective of this article is to review the current understanding of NCSE, heighten awareness of the condition, and ultimately improve the care these patients receive.

Definitions

The Epilepsy Research Foundation's proposed definition for nonconvulsive status epilepticus is: "A range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms" (1). At first glance, this does not seem a useful definition, and yet it reflects the difficulty faced by the workgroup in finding commonalities between the wide range of disorders that result in NCSE. The definition builds off of past definitions that characterized NCSE as a state of continuous or intermittent seizure activity without a return to baseline, lasting more than thirty minutes. Historically, thirty min-

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utes has been used as a defining feature for status epilepticus, yet the time is arbitrary and recent definitions of status epilepticus have used time frames as short as five minutes (3). In general, NCSE differs from convulsive status by the lack of a predominant motor component (4). The hallmark of NCSE is a change in behavior or mental status that is associated with diagnostic EEG changes.

There are two main categories of NCSE: absence status, which is a primary generalized process, and complex partial status, which is focal in origin. A third category is subtle generalized convulsive status epilepticus, which describes a subset of patients who have sustained significant cerebral insult, often after an episode of convulsive status epilepticus, and are in a comatose state that is at least partially due to ongoing seizure activity (5). Since the etiology and prognosis of subtle convulsive status is distinctly different from that of AS and CPS, it will not be further discussed in this article.

Both absence and complex partial status are characterized by a change in the level of consciousness and behavior, with either no or minimal motor activity. Onset can be sudden or gradual, and the duration can vary from minutes to days or months (6). Unresponsiveness, once thought to be a distinctive feature of CPS (7), has also been described in association with absence status (8, 9); the same is true for cyclic patterns (4). Absence status is usually characterized by abrupt clearing of consciousness, though gradual postictal normalization has been reported (6). CPS is usually followed by a prolonged postictal state with depression.

Historically, absence status was reported to be more common than complex partial status but improved electroencephalographic techniques have brought this into question (4, 10). Rapid generalization of CPS on EEG is the most likely explanation for misdiagnosing cases of CPS as absence status, possibly compounded by unawareness of this issue (4, 11). Supporting this concept are reports of AS responding to pharmacologic interventions that are usually not indicated in AS (e.g., phenytoin and phenobarbital); it is possible that in these cases the actual diagnosis was CPS with rapid generalization (12).

In summary, clinical manifestations of AS and CPS overlap significantly and there are no clear clinical criteria that accurately differentiate the two. The overlap in clinical presentations and the potential for rapid generalization on EEG poses a challenge in clinical decision making.

Epidemiology

Establishing the incidence of NCSE is challenging since the diagnosis requires availability of an EEG. Most of the studies in the literature include only hospitalized patients, and even in those studies there is a selection bias, i.e., if the diagnosis had not considered, the EEG was not obtained. It is easier to establish the incidence of generalized convulsive status epilepticus (GCSE) since its clinical manifestations are recognizable: In a population based study, DeLorenzo et al. report an incidence of 41 per 100,000. Population-based epidemiological studies have indicated mortality from GCSE to be almost 22%, and that figure can increase to 30% in the elderly (13).

Regarding NCSE the Epilepsy Foundation Research workgroup amalgamated the data from the literature and reported an estimated incidence of 6–18 cases / 100,000 / year (1). Towne et al., in a prospective study of 236 patients with coma who had no clinical evidence of seizures, reported that 8% of the patients met criteria for NCSE on EEG (11); DeLorenzo et al. found that NCSE was present in 14% of patients after control of GCSE (13). In a prospective population-based study of status epilepticus, NCSE represented approximately 5% of status epilepticus cases presenting in Richmond, Virginia (14). Privitera and Strawsburg reported that in a prospective study of 198 patients with altered consciousness, 37% had EEG findings suggestive of NCSE (15). These studies emphasize the need to keep NCSE in the differential diagnosis of any patient with altered mental status when the etiology is unknown: These studies also bring to light the question of whether electrophysiology should be available 24/7.

NCSE has been reported in all age groups from the very young to the very old and in both sexes without a clear predominance in either sex (11, 16, 17). NCSE does not require a prior history of seizures, with the literature reporting that 10–100% of patients who present with NCSE having no history of a seizure disorder (4, 6, 7, 9, 17–19). It is estimated that 10% of adults with absence seizures will have at least one episode of absence status (6, 20). Though absence status has mostly been reported in children it can present *de novo* in later life (18, 21).

A variety of precipitating factors have been implicated in NCSE including metabolic abnormalities, infection, drug toxicity, alcohol intoxication / withdrawal, pregnancy, central nervous system (CNS) lesions, and electroconvulsive therapy treatment (8, 21, 22). Different series have identified a precipitating factor in 15–70% of cases, emphasizing the importance of a comprehensive assessment in the evaluation of these patients (7, 10).

Clinical Characteristics

Clinical manifestations of NCSE include the full spectrum of mental status changes. Findings can be so subtle that they are recognized only by family or by friends, while at the other end of the spectrum these patients can appear delirious or in coma; see Table 1 (6, 2, 7, 11, 23–29). Fluctuations of symptoms can occur with varying degrees of impairment, which at times contributes to obscuring the diagnosis.

Motor activity is normal in most cases; however, decreased response time, clumsiness, apraxia, focal jerks, twitching of facial muscles (in particular of the eyelids and automatisms such as licking, chewing or picking) have been reported (4, 30). When present, automatisms have been thought to be longer in duration and more complex in nature in CPS than in AS (31, 32). Automatisms in the form of gross movements such as positioning, raising, flexion or extension of the extremities, head deviation, though not common, have also been noted (4).

In view of the panoply of clinical presentations, it becomes clear how challenging this diagnosis can be in any circumstance, but especially with a patient who presents with cognitive impairment at baseline (e.g., mental retardation or dementia) or who carries a prior history of a psychiatric disorder.

Diagnostic Approach

The differential diagnosis of altered mental status is extensive, and being able to determine the underlying cause on clinical grounds alone is at times almost impossible. Table 2 lists some situations in which a diagnosis of NCSE should be considered. After reviewing the wide range of presentations of NCSE, it is easy to understand how the diagnosis is often missed and confused with a psychiatric disorder or a neurologic insult. In order to put the patient's presentation into the proper context, a detailed history needs to be obtained, including change from baseline status, onset and duration of the events, presence or absence of lucid interval, timing in relation to the sleep/wake cycle, and presence or absence of motor activity or automatisms. Medical, neurologic and psychiatric history, family history, social history, and medication history are other important components of the diagnostic evaluation.

TABLE 1

Clinical Presentations of Patients in Nonconvulsive Status Epilepticus

- Mild cognitive disturbances (e.g., impaired attention, difficulty in sequential planning of complex motor tasks)
- Mild disorientation or confusion
- Prolonged confusional states
- Mood disturbance
- Cortical blindness
- Speech disturbance (e.g., verbal preservation, reduced verbal fluency, muteness, speech arrest or aphasia)
- Echolalia
- Confabulation
- Bizarre behavior that is uncharacteristic or deviates from baseline (e.g., laughing, dancing and singing inappropriately)
- Psychotic states
- Autonomic disturbances (e.g., belching, borborygmi, flatulence)
- Sensory and psychic phenomena
- Coma

TABLE 2

Situations Where Nonconvulsive Status Should Be Considered

- Prolonged postictal period (more than two hours) after a generalized tonic-clonic seizure
- Altered mental status associated with twitching or blinking and/or fluctuating mental status
- Altered mental status of unexplained etiology, especially in patients with a history seizures
- Unexplained altered mental status in the elderly
- Stroke patients who look clinically worse than expected

Currently, there are no clear criteria for deciding when an EEG should be requested. That said, when NCSE is suspected on clinical grounds, an EEG is indicated to confirm the diagnosis and direct management. Table 3 lists the types of EEG patterns identified by the Epilepsy Research Foundation's workshop (1).

In absence status, EEG is characterized by continuous or nearly continuous generalized, rhythmic, bilaterally synchronous, spike-and-wave discharges at intervals of 3/second with a maximum over the bifrontal region; however, variations in the EEG pattern can occur, including 2–3 per

TABLE 3

Electrographic Criteria of Nonconvulsive Status Epilepticus

- Frequent or continuous focal electroencephalographic seizures
- Frequent or continuous generalized spike wave discharges in a patient without a prior history of epilepsy
- Frequent or continuous generalized spike discharges which show significant changes in intensity or frequency compared to baseline EEG
- Periodic lateralized, or periodic bilateral, epileptiform discharges occurring in patient in coma after a generalized tonic clonic seizure
- Frequent or continuous EEG abnormalities in patient with no previous similar abnormalities
- Frequent or continuous generalized EEG abnormalities in patients with epileptic encephalopathies in whom similar interictal EEG patterns are seen but in whom clinical symptoms are suggestive of nonconvulsive status

second spike-waves complexes as well as bursts of rhythmic slow, rhythmic or arrhythmic spike waves or polyspike activity (4, 17, 33, 34). In CPS, various forms of less synchronous seizure activity, rhythmical slowing, rhythmic spikes, and rhythmic sharp and slow waves have been described (4, 30, 26). One should be aware that while several EEG patterns have been described to be suggestive of both types of NCSE, a clear pathognomonic pattern has not been defined. When (and if) an EEG is performed at the onset of the seizure, a clear focus may be identified that may be critical to differentiating CPS from AS. If secondary generalization is present, either because of rapid spread or because the EEG is performed when a patient has been in CPS for a long period of time, then there is the risk of misclassification (4, 35). This has significant clinical implications since long-term pharmacologic management is different for primary and secondary generalized seizure disorders.

Case Presentations and EEG

Case #1

On the second hospital day, a 68-year-old man with a small bowel obstruction was found unresponsive to both verbal and painful stimuli. He had no other medical problems. The obstruction was secondary to adhesions from past surgery. He was taking no medications. His physical and neurologic examinations were non-focal. An EEG was obtained (Fig. 1). The EEG shows bilateral, asynchronous, almost continuous sharp wave discharges, which improved with 2 mg of lorazepam.

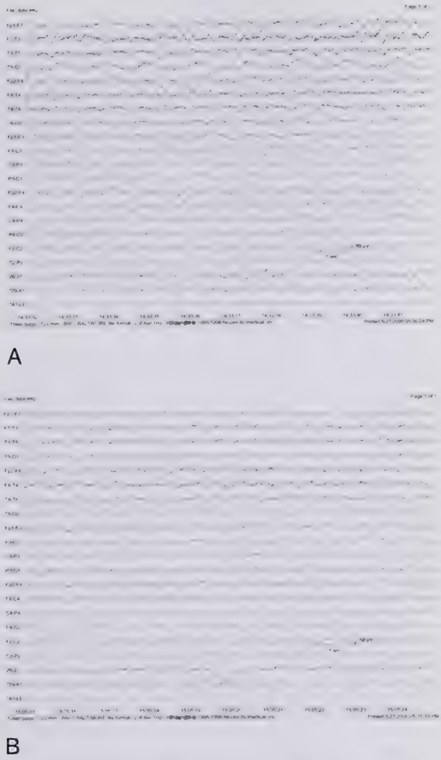

Fig. 1. EEG of a 68-year-old man with a small bowel obstruction: **(A)** before medication and **(B)** after 2 mg of lorazepam. EEG and case courtesy of Dr. James Rowan.

Case #2

An 83-year-old woman with no history of seizure disorder developed a fever of 102°F. She developed a seizure characterized by focal left arm twitching followed by secondary generalization. The seizure lasted several minutes but the patient remained "post-ictal" for hours after the event leading to obtaining an EEG (Fig. 2). The EEG shows generalized bilaterally synchronous sharp waves at 2/second, which resolved after a loading dose of phenytoin was given.

Prognosis

Prognosis of NCSE is dependent on the underlying etiology; however, good research in this area is limited. Without characterizing the type and etiology of NCSE, it is not possible to assign a predictable outcome. Outcomes do not appear to be as closely linked to duration of the event as in generalized convulsive status.

Prognosis is dependent on the population and type of NCSE; for example, elderly patients in subtle generalized status have an extremely poor prognosis and studies on this group recommend aggressive therapy (36). Shneker and Fountain found that in patients who had an acute medical problem as the underlying cause of NCSE, overall mortality was as high as 27% (37). A study of elderly patients with NCSE concluded that a prognosis NCSE for an elderly patient was worse because of the severity of the underlying etiology and because of hospital-acquired infection (38). On the other hand, other series on patients with CPS and AS suggest that NCSE is a relatively benign condition (37). Indeed, there is a report in the litera-

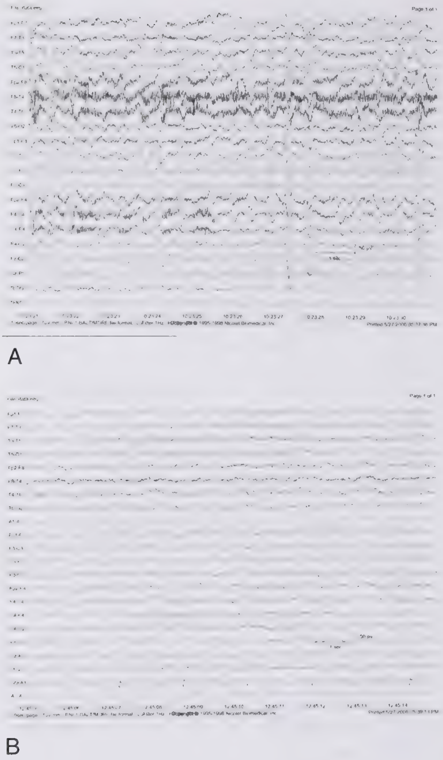

Fig. 2. EEG of an 83-year-old woman who developed a seizure: **(A)** before medication and **(B)** after loading dose of phenytoin. EEG and case courtesy of Dr. James Rowan.

ture of a case where NCSE lasted nine years, in which the patient did not exhibit any definite cognitive changes (39).

The question regarding prognosis relates to distinguishing between the reversible cognitive impairment that resolves when the NCSE is treated and permanent damage that results from the ongoing and persistent neuronal discharges. Since most patients do not have both pre- and post-seizure neurocognitive testing, it is difficult to ascertain cause and effect. However, studies looking of markers of brain injury suggest that NCSE does predispose to permanent injury at some level (1). In convulsive status, even when systemic effects are controlled with paralysis and ventilation, CNS damage in the hippocampus (40, 41) occurs relatively quickly. The mortality rate ranges form 5–50% (42); in this case aggressive treatment is advocated since it is thought that the outcome is related not only to the underlying etiology of the episode but to its duration (32). In NCSE, it has been suggested that neuronal damage may occur (42), but controversy still exists regarding the need for aggressive therapy since there are reports of both complete recovery and of associated transient or permanent cognitive or neurologic deficit (28, 43).

The limiting factor in better assessing the true morbidity and mortality of NCSE is due to the variety of clinical symptoms, potential misinterpretation of EEG patterns, grouping of patients with different comorbities, and lack of prior cognitive function or neuropsychological assessment for comparison. Due to the lack of well-designed studies there are still no clear guidelines for the treatment of NCSE and there is still significant controversy regarding the need for aggressive therapy.

In summary, the data suggests that prognostically NCSE generally does not result in permanent cognitive or neurologic deficit unless it occurs in the setting of an underlying medical problem. Further controlled prospective studies and clear guidelines are needed for the management of these difficult patients.

Treatment

Despite several controversies regarding the importance of the timing in initiating treatment in NCSE, general principles in the management of NCSE include early identification of etiological and precipitating factors so that they can be corrected as soon as possible. Physiological stressors, including infections, toxins, metabolic abnormalities, structural lesions, drug interactions or withdrawal and pregnancy, should be sought in all patients presenting with either a new seizure or exacerbation of a known disorder.

NCSE had been identified for more that 50 years, though to this day it is still unknown if the morbidity that can occur in NCSE is secondary to NCSE *per se* or if it is secondary to underlying conditions. Clear guidelines have not been established on the importance of the timing in initiating treatment, choice of anticonvulsants, or how aggressively we should institute treatment, especially in case of treatment resistance. Ultimately, after a careful risk/benefit assessment, treatment is tailored to the individual situation. In order to assess any correlation between the EEG pattern and clinical symptoms, intravenous benzodiazepine should be administered during EEG monitoring. Confirmation of NCSE by EEG is recommended before instituting pharmacological treatment, whenever possible. Some clinicians have opted to give benzodiazepine without EEG guidance when NCSE is clinically suspected, however, the pros and cons involved in this practice must be carefully weighed.

There have been cases described in the literature were spontaneous recovery or immediate response to i.v. benzodiazepines has been observed (13), although episodes of NCSE often tend to reoccur and require an additional anticonvulsant. The questions that are still unanswered are which anticonvulsants should be used as a second or third line treatment, how aggressive the treatment should be, and how to balance the risks and benefits of treatment.

Benzodiazepines, e.g., diazepam (4, 7), lorazepam (44), clonazepam (4), and midazolam (3), have all been used as monotherapy or in combination. It has been shown that NCSE responds to benzodiazepine, even if at times the response is delayed, or followed by a recurrence of symptoms hours or days later; therefore, the use of long-acting antiepileptic drugs (AED)s may be required in order to achieve lasting effects (4, 28).

Benzodiazepines are particularly indicated in case of *de-novo* absence when the precipitating factor is secondary to benzodiazepine withdrawal (21), or in cases of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (Melas syndrome), in which case valproate and phenytoin are not viable choices (45). The use of benzodiazepines should be carefully assessed in patients who are medically compromised and in whom possible hypotension or respiratory depression may occur. Of note, it has been reported that the response to i.v. benzodiazepines can be different in AS vs. CPS, in that it the former the response has been reported to be more abrupt, whereas in the latter it is more variable (44).

Once the diagnosis of NCSE is determined and seizures controlled, long-term treatment should be considered. Several antiepileptic drug options are available. Phenytoin, valproic acid, and phenobarbital have all been suggested. They can be administrated intravenously in the attempt to control an acute event or orally when long-term treatment is required. Carbamazepine, primidone, and the new generation AEDs (e.g., lamotrigine, topiramate, levetiracetam) are also considerations for long-term treatment. Valproic acid is the drug of choice for managing patients with absence seizures (46). Ethosuximide and clonazepam have also been used (47). Vigabatrin and tiagabine have not been recommended due to concerns that they might play a role in worsening or precipitating NCSE (48).

Conclusion

Nonconvulsive status epilepticus is more common than once appreciated and should be considered in any patient presenting with an alteration in mental status of indeterminate etiology. Table 4 lists the key points that summarize concepts presented in this article. The clinician must remain aware of the different clinical characteristics of this disorder and remember that a seizure history is not necessary for the diagnosis, nor is there necessarily associated motor activity. The diagnosis is confirmed with an EEG, which is required in order to distinguish absence status from complex partial status. Treatment begins with correcting underlying etiologies and using a benzodiazepine. Response can be delayed, in which case other anticonvulsants are indicated. The overall prognosis is generally good for both AS and NCSE, although the literature is unclear if neurocognitive outcomes are related to duration of the status. There is still a great deal that is unknown about NCSE, and a need for well-designed studies in both diagnosis and therapeutics.

TABLE 4

Key Concepts in Nonconvulsive Status Epilepticus (NCSE)

- Nonconvulsive status epilepticus is characterized by altered mental status ranging from subtle memory deficits to coma
- Prognosis in NCSE is related to etiology
- Altered mental status or coma of undetermined etiology and prolonged "postictal" periods should prompt an investigation of NCSE
- Treatment of absence status and complex partial status is less emergent and less aggressive than for convulsive status epilepticus
- NCSE persisting after the treatment of convulsive status epilepticus portends a poor prognosis
- Benzodiazepines are the first-line treatment for NCSE

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Women's Cognitive and Affective Health and Neuropsychiatry

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Abstract

Recent interest in women's health has focused on the cognitive consequences of aging and hormonal changes. Based on hypotheses about estrogenic effects in the central nervous system (CNS), large-scale clinical trials were designed to address the efficacy of hormone replacement on protection against dementia and cognitive decline. Surprisingly, an absence of risk reduction for dementia and cognitive loss was found and much reanalysis of these findings has focused on timing of hormone replacement. Here we take a broad perspective to address a fuller range of psychological health. Gender differences in other psychiatric conditions including depression and anxiety have been attributed to hormones, and the neurotransmitter systems that are implicated in affective disorders may have an impact on cognitive impairment as well. Hormonal influences on neurotrophic mechanisms, as well as neurotransmitter effects, may be responsible for a breadth of neuropsychiatric conditions, particularly in aging.

This review will focus on cognition, mood and anxiety issues among women, with an emphasis on changes associated with aging. We will review data on the epidemiology of these entities and examine the biological mechanisms that may be involved, with an emphasis on those mechanisms that may contribute to the multiple aspects of neuropsychiatry and women's health.

Key Words: Women's health, cognition, affect, estrogen.

Introduction

THE PAST DECADE has brought a focus on many aspects of women's health. In neuropsychiatry, there has been specific interest in cognitive and affective health of women as they age. Much of the work in this field has focused on the consequences of estrogen reduction through menopause and the effects of hormone replacement.

Both affect and cognition may be mediated through neurotransmitter manipulations, specifically acetylcholine and serotonin, and estrogen has been shown to have a wide range of effects on both of these systems. Much of the data supporting a clinical benefit of estrogen has come from observational studies of women during menopause, when estrogen levels are reduced. Other observational studies have examined the effect of estrogen replacement therapy (ERT) on cognitive and affective outcomes. Recently, well-controlled clinical trials have been completed with results that do not confirm some of the observational studies. However, it is not clear how well ERT can improve cognitive complaint and affective disturbances. In addition, recent studies have examined non-estrogenic approaches to intervention for depression as well as a combination of estrogen and other agents to determine the spectrum of benefit from hormone replacement.

Below, we examine the epidemiology and neurobiology of cognitive and affective disturbances in women as they transition through menopause. We will also take an evidence-based approach to the review of therapeutic options to treat these neuropsychiatric conditions. We begin with a review of the changes of menopause and mechanisms of neurobiological effects.

Menopause

Currently in the U.S., the mean age of menopause is 51 years, and the perimenopausal period begins at a mean age of 47.5 years (1). Perimenopause is defined as the period when menstrual cycles become irregular, follicle-stimulating hormone (FSH) rises as the ovary becomes unresponsive to pituitary stimulation, and there is a

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breakdown in the usual cycle of the hypothalamic-pituitary-ovarian system. Perimenopause is diagnosed even pre-symptomatically if FSH is above 25 IU/L and estrogen less than 40 pg/mL when drawn during the early follicular phase. During this time, there are fluctuations in the levels of gonadal steroids, with initial increase, then marked decrease in estradiol levels. Progesterone, another ovarian androgen, also decreases. Menopause is completed one year after the last menstrual cycle, at which time the post-menopausal phase begins.

The drop in estrogen begins during late perimenopause and is sustained during post-menopausal years without hormone replacement therapy (HRT), conferring a state of relative estrogen deficiency. The change in estrogen level seems to play a role in the physiological, cognitive, and affective vulnerabilities of this transitional period; however, once the transition is complete rates of depression improve and become stable again. While cognitive complaint is common in perimenopause and menopause, there has been less success in documenting this deficit with formal testing. However poor, cognitive deficit increases with age and it has been suggested that persistent estrogen deficiency may contribute to these cognitive deficits.

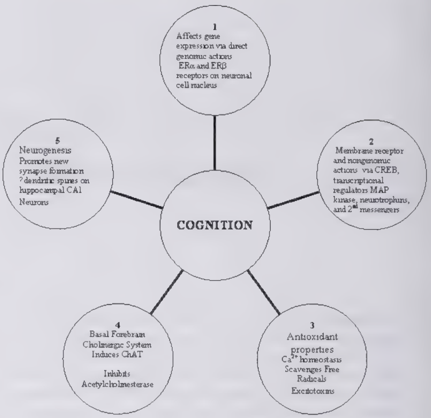
1
Affects gene expression via direct genomic actions ERα and ERβ receptors on neuronal cell nucleus
2
Membrane receptor and nongenomic actions via CREB, transcriptional regulators MAP kinase, neurotrophins, and 2nd messengers
COGNITION
3
Antioxidant properties
Ca2+ homeostasis
Scavenges Free Radicals
Excitotoxins
4
Basal Forebrain Cholinergic System
Induces ChAT
Inhibits Acetylcholinesterase
5
Neurogenesis
Promotes new synapse formation
? dendritic spines on hippocampal CA1 Neurons

Fig. 1. The neurobiology of the effective role of estrogen on cognition.
ChAT = choline acetyltransferase, MAP = mitogen-activated protein, CREB = camp response element-binding [protein].

Estrogen May Have Neurobiological Effects

Estrogens are steroid hormones with a multiplicity of actions that can have an impact on cognition. This is outlined in Fig. 1. Estrogens act on receptors located in the cell nucleus and affect gene expression. There are two estrogen receptors, Erα, which appears to be important in cognition and has been associated with estrogen's effect on cognitive processing, and Erβ, which has been associated with effects on the serotonergic system and emotional processing. Furthermore, there are also membrane receptors on dendrites, presynaptic terminals and glial cells (2). There are several brain areas associated with cognition in which estrogen appears to have effects, including the basal forebrain cholinergic system, from which neurons project to the cerebral cortex and hippocampus. In this area, estrogen induces choline acetyltransferase (ChAT), which is the rate-limiting enzyme in the synthesis of acetylcholine (2). Other effects of estrogen include trophic effects such as enhancement of insulin-like growth factor-1 receptors, neurite outgrowth and cytoprotection from oxidative damage (2). Estrogen has an important influence in the hippocampal synaptogenesis and is associated with increased dendritic spine density on pyramidal neurons. Estrogen may also have effects on neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which affects neuronal differentiation, survival and synaptic plasticity. In addition to its direct trophic effect on the cholinergic neurons, estrogen may facilitate serotonin-mediated acetylcholine release in the frontal cortex through the 5-HT_{1A} receptor (3). Long-term estrogen replacement enhances serotonin-stimulated acetylcholine release in the adult rat frontal cortex (3). Animal studies suggest that a state of chronic estrogen deprivation is characterized by reduced BDNF in some cortical and hippocampal areas and that these changes are reversible only if estrogen is provided within a certain period of time. This data may be important to recall as clinical studies are evaluated below (4).

The neurobiology of the affective role of estrogen has also been studied and this multiply determined interaction is summarized in Fig. 2. The ERβ receptor has been associated with effects on the serotonergic system and emotional processing. In support of this, ERβ knockout mice show increased anxiety symptoms, modeled by the fear-like "amygdale-response," possibly through the serotonergic system. Tamoxifen, an ERβ blocker, prevents estrogen-induced increase in the serotonergic 5-HT_{2A} receptor mRNA in the dorsal raphe nucleus and binding in the frontal cortex, anterior cingulate, primary olfactory cortex, striatum and nucleus accumbens (5). These areas have also been associated with mood and the fear response. Acute 17β estradiol treatment downregulates both the 5-

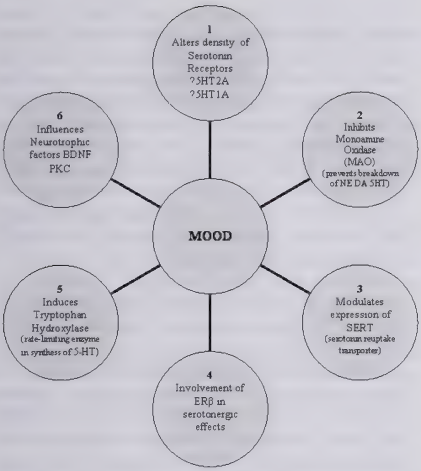

Fig. 2. The neurobiology of the effective role of estrogen on mood.
BDNF = brain-derived neurotrophic factor, PKC = protein kinase C, NE = norepinephrine, DA = dopamine.

HT_{1A} receptor mRNA and the 5-HT_{1A} receptor in these limbic areas of female rat brain, but the effect is diminished with chronic treatment (2 weeks). Stimulation of the 5-HT_{1A} autoreceptor is known to reduce the firing rate of the serotonergic neuron. Studies have suggested that estrogen causes sensitization of postsynaptic 5-HT_{1A} receptors in the hippocampus, and desensitization of the presynaptic 5-HT_{1A} receptors in the dorsal raphe (5), which predicts a different time course for modulation of cognition and affect.

In laboratory studies, estradiol has been found to inhibit serotonin reuptake transporter (SERT) mRNA, and receptor and transporter protein activity (6). One of the ways estrogen increases serotonin levels is by increasing production of tryptophan hydroxylase, the enzyme responsible for the rate-limiting step in serotonin production. By inhibiting expression of the gene for SERT, estradiol acts as an antagonist of this transporter, in some ways similar to the selective-serotonin reuptake inhibitor (SSRI) (7). 5-HT_{1A} receptors are downregulated by both estradiol and antidepressants (8).

Serotonin and Cognition

Cognitive processes are modulated by neurotransmitter systems via ascending monoamine projections to the prefrontal cortex and investigations are beginning to reveal the role of serotonin in various aspects of cognition. Neurotransmitter systems including serotonin play a role in regulation of executive functions mediated through the dorsolateral prefrontal cortex, which are responsible for working memory and attentional set shifting. Estrogen can induce changes in serotonin transmission, binding and metabolism in brain regions that are involved in these frontal areas, thereby affecting memory and affect (3). Serotonin is thought to play a role in hippocampal-based learning (2). Estrogen and progesterone, another important hormone, may have a variety of effects on neurotransmitter systems, including those with norepinephrine and dopamine as well as gamma-aminobutyric acid (GABA), all of which may have cognitive and behavioral influences. For a review of these mechanisms see McEwan, 2001 (2).

Cognition, Women and Aging

Cognitive complaint may occur in women regardless of menstrual status, but clearly increases with age with up to 40% of women between the ages of 48 and 55 complaining of forgetfulness. Many, but not all, of these complaints are associated with menopausal symptoms. However, it has been difficult to document cognitive deficits with neuropsychological testing in both peri and early postmenopausal women. One recent investigation, a birth cohort study of 1,261 women, did find weak evidence of an adverse effect of natural menopause on cognitive function, but this effect was largely explained by pre-menopausal cognitive functioning. Cognitive deficits in this prospective observational cohort were not associated with vasomotor or psychological symptoms and were not associated with a benefit with estrogen replacement. Large cross-sectional studies, however, have failed to find an association between reproductive period, as a surrogate measure of endogenous estrogen exposure, and cognitive performance (9). (For a fuller review and meta-analysis of epidemiologic studies and small clinical trials, see LeBlanc [10]).

Existing studies have not adequately separated the effects of aging on cognition from the potential effects of menopause. Also, other symptoms associated with menopause (e.g., sleep disturbance) may indirectly contribute to cognitive symptoms.

Cognitive Complaint in Younger Postmenopausal Women

There have been several randomized controlled trials examining the effects of unopposed estrogen (typically estradiol or conjugated equine estrogen [CEE]) on cognitive functioning in younger (<65 yrs of age) post-menopausal women (11 – 19) (see LeBlanc et al. [10] for review). Many of these studies had small sample sizes and the duration of use was uniformly short, ranging from 21 days to 6 months. Methodological differences in study design (i.e., cross-over vs. separate experimental and placebo groups); preparation and dose of HRT; cognitive outcome measures; type of menopause (i.e., surgical vs. natural); whether or not women with menopausal symptoms were included; and prior estrogen use made it impossible to combine these trials quantitatively in a meta-analysis.

Nevertheless, some trends were apparent. First, no deleterious effects on cognitive functioning were observed. Second, hormone therapy did not consistently enhance cognitive test performance in women who were not experiencing menopausal symptoms. Among women with menopausal symptoms, however, ERT improved cognitive test performance, especially on tests of verbal memory and attention, as well as abstract reasoning and motor speed (10). Third, the effects are most robust in cohorts who have undergone surgical menopause and are less evident in those undergoing natural menopause. Although not examined directly, it is possible that the cognitive improvement observed in symptomatic women receiving HRT may be attributed to a lessening of other menopausal symptoms (e.g., hot flashes, sleep disturbance, mood changes). Nevertheless, it appears that cognitive improvement—at least in the domains of verbal memory and attention—may be an additional benefit of ERT for these younger women.

Most of the above work was conducted before it became apparent that estrogen should be co-administered with progestational agents to protect the intact uterus from hyperplasia. There have been only two studies to date examining the effects of estrogen progestin combination regimens on cognition in younger women, and they were based on the same cohort of 49 women (20, 21). These 2 studies were designed to compare 3 groups: unopposed estrogen (estradiol valerate), opposed estrogen (estradiol valerate plus dienogest), and placebo. Results revealed that women randomized to unopposed estrogen performed better than the other two groups on a test of verbal learning, while those receiving opposed estrogen performed better on a test of numerical memory.

Clinical Considerations

Since combination therapy is the standard of care for women with an intact uterus, the data leaves us in clinical equipoise, with so few studies examining cognitive effects of opposed estrogen therapy. When this prevalent and clinically relevant group has cognitive complaint, it is difficult to know how to counsel them. If they also have menopausal symptoms, the recommendation for HRT is clearly indicated, but the long-term effect on cognition in this young group is not clear. However, since the data from women over the age of 65 is not supportive of cognitive benefit and is associated with other health risks, it seems reasonable to minimize long-term exposure.

Cognitive Complaint in the Older Postmenopausal Women

Observational studies indicate that estrogen use was associated with a reduced risk of dementia in general and Alzheimer's disease specifically (10, 22). Two meta-analyses of these studies were relatively consistent with approximately a 30% reduction in risk reported by each study. The promise of these observational studies led to an ancillary study by the Women's Health Initiative (WHI) hormone therapy trials, the Women's Health Initiative Memory Study (WHIMS) (23). This sub-study enrolled women aged 65 or older who were free of probable dementia at baseline, from the placebo-controlled, randomized WHI trial, Treatment regimen for the combination hormone therapy was 0.625 mg/day CEE and 2.5 mg of medroxyprogesterone acetate for women with a uterus, and CEE alone for those who had had a hysterectomy. Primary outcome measures of this study were incident dementia and mild cognitive impairment (MCI), defined as performance at or below the 10th percentile in at least 1 area of cognitive function. Secondary analyses examined global cognitive function as assessed by the Modified Mini-Mental State Examination 3MSE. Disappointing results from WHIMS revealed a two-fold increased risk of dementia for women in the estrogen plus progestin group (24). This increased risk translated into an additional 23 cases of dementia per 10,000 women per year. Although the treatment groups did not differ in their risk of developing MCI, a condition thought to be a prodrome to dementia, the secondary outcome of performance on global cognitive function revealed that scores in the treated group had statistically smaller improvements than those in the placebo group.

Results from the Unopposed Estrogen Trial, which had a smaller sample size, did not reveal significant effect of treatment on incidence of dementia or on global cognitive function. When data are combined to include those with and without medroxyprogesterone, a dramatic decline was observed among women who scored poorly on the cognitive test at their screening visit. This suggests that hormone therapy may have accelerated an existent disease process. This finding parallels that seen in women with dementia, in whom several clinical trials have demonstrated no benefit or cognitive worsening with estrogen (25–27).

Clinical Considerations

Despite suggestions from observational studies that hormone therapy may play a role in maintaining cognitive health and preventing Alzheimer's disease in older women, findings from the WHIMS have demonstrated clearly that—at least in women age 65 and older—there were no cognitive benefits of CEE, with or without medroxyprogesterone (MPA). Women randomized to active therapy scored lower on a measure of global cognitive functioning and were more likely to develop dementia or mild cognitive impairment. The increased risk of cognitive decline in women randomized to hormone therapy may be due to the vascular effects of estrogens (e.g., increases in thrombin, fibrinolysis, triglycerides, and C-reactive protein) and associated vascular disease in the brain; the high incidence of stroke in patients in both the CEE and CEE+MPA trials supports this claim (28). It is unclear whether the results from the WHIMS will generalize to other hormone preparations; however caution seems warranted in prescribing any hormone replacement therapy to healthy older women for the purpose of preventing cognitive decline.

Affective Disorders in Women

The lifetime prevalence of depression is 17% overall, and the prevalence in women is twice that in men (29). High-risk periods for the development of depression in women occur when there are significant hormonal shifts. The risk is highest in the period from puberty to menopause, (i.e., the reproductive years). In the prepubertal and postmenopausal stage, depression risk is actually lower. In fact, during these phases rate of depression among females is approximately the same as that of males.

The three periods of rapid hormonal fluctuation and increased susceptibility to affective changes (primarily depression) are premenopause, post-partum, and perimenopause. The psychoemotional symptoms thought to be associated with menopause overlap with depressive symptoms and include disturbed sleep, concentration, anxiety, irritability, frustration, mood lability, depression, and fatigue (30). Two epidemiologic prospective studies examined the onset of major depression during the menopausal transition and found increased susceptibility during that time (31, 32). Freeman described an increased risk for first-onset clinically significant mood disturbance in perimenopausal vs. premenopausal women (32). In his report, which followed 29 perimenopausal women for 5 years until 6 months after last period (33), Schmidt found that the 24-month period around menopause carried a 14-fold increase in the risk of depression.

There are several factors that appear to increase the risk of depression during the peri-menopause. They include a history of depression (33–36) and a history of premenstrual syndrome (32, 37). Other features associated with menstrual history that appear to increase the risk of depression are reduced parity (36), longer duration of perimenopause (defined as the duration of irregular cycles), presence of hot flashes, and history of post-partum or premenstrual depression. Other social factors that have been associated with depression during this period are non-specific and include stressful life situation, poor health, history of smoking, sleep disturbance and absence of a partner.

The menopausal transition, marked by perimenopause, has been identified as an independent risk factor for depression (36). The frequent coexistence of hot flashes and depression (35, 38) has been thought to reflect an underlying CNS response to estrogen deficiency. The brain's thermoregulatory system involves serotonin's 5-HT_{2A} receptors, which decrease in density with the decline in estrogen, thereby implicating serotonin in both affective and vasomotor symptoms. The connection, also supported by the results of a large study, suggest that indicated that perimenopausal period from early menopause to 1 year after the last menses is associated with an increased risk of depressive illness; however, the postmenopausal time is not (36). In terms of major affective disorder, two epidemiologic prospective studies examining the onset of mood disorders during the menopausal transition provide evidence of increased susceptibility during this period (31, 32). Freeman described an increased risk for first-onset, clinically significant mood disturbance in perimenopausal vs. premenopausal women (32). Schmidt found that the 24-month period around menopause carried a 14-fold increase in the risk of depression.

The vulnerability conferred by hormonal shifts may not necessarily mean that low estrogen is the only etiologic factor. The finding of depression onset in early perimenopause (when estradiol levels are actually elevated) and the fact that estrogen and androgen levels in patients with perimenopausal depression do not differ consistently from those of controls (39, 40) suggests that estrogen itself is not the only factor in depressive perimenopausal states. It may be the balance among fluctuating hormones that contributes to affective disturbance.

Estrogen as a Treatment for Affective Disorders.

Several lines of evidence suggest that estrogen may have a mood-elevating effect. Depression during hormonal transition can be seen even in patients without a history of depression (1, 41), and several studies have addressed the issue of whether or not estrogen replacement can improve depression. There is evidence for estrogen's antidepressant effect in depressed perimenopausal patients (42, 43). In the two major randomized, placebo-controlled trials of transdermal estradiol therapy for perimenopausal depression, 60–75% of subjects vs. 20–30% of subjects taking placebo obtained partial or total remission of depressive symptoms (42, 43). In addition, in a pilot study of estrogen augmentation for antidepressant treatment in perimenopausal females (n=17), mood was improved with addition of 0.625 mg estradiol and there was a significant decline in Hamilton Depression Scale (HAM-D) over a 6-week period (p=0.012) (44).

The effect of HRT may differ among peri- and postmenopausal women. To determine if HRT could reduce severity of depressive symptoms among depressed postmenopausal women, Goldstein examined data from 1,160 women aged 60 and older with a diagnosis of major depression or dysthymia who were enrolled in the IMPACT study (45). At baseline, 44.5% of the sample was on HRT; this subgroup tended to be younger, white, married, educated with better health, and more likely to report antidepressant use in the previous 3 months. The group on HRT did not differ statistically from non-HRT users in depression severity as measured by the Symptoms Checklist—90 items (SCL-90). In this study there was no evidence that HRT modified the severity of depression (45).

There is substantial clinical and laboratory evidence suggesting that estrogen may be an important mediator of affect. A placebo-controlled, double-blind study by Heinrich and Wolf examined whether women who are estrogen deficient but not depressed might benefit from the boost in neurotransmitters that laboratory evidence suggests estrogen may produce (46). In their study, 51 women with a mean age of 64 years, who were stable in a postmenopausal state (they had had hysterectomies a mean of 13 years prior and were not on HRT) were randomized into three groups to receive estrogen, estrogen/progesterone, or placebo for a 24-week trial. The dose of estrogen in this study was quite high: the combined HRT consisted of estradiol 2 mg/progesterone 100 mg daily and ERT dose was estradiol 2 mg daily (44). Outcome measures were assessed at baseline, 4 weeks and 24 weeks, and included mood, well-being, menopausal symptoms, depression and subjective sleep. Thirty-five of 51 completed the trial and the findings were that neither hormonal intervention was more effective than placebo on the outcome measures. However, the fact that the subjects were not depressed at baseline yielded ceiling effects on the outcomes, making it difficult to observe any benefit.

Almeida considered the possibility that HRT, which combines the potentially antidepressant estrogen with progesterone (which can be a depressant), masks the beneficial effect of unopposed estrogen treatment (47). In a randomized, double-blind, placebo-controlled trial of 20 weeks, the effect of supplemental unopposed estrogen on the mental health outcomes of healthy women older (70+) at risk was examined. A total of 115 women were randomized to estradiol 2 mg or placebo for 20 weeks. The outcome measure of Beck Depression Inventory, quality of life (QOL) by the 36-item short form health study (SF-36) scale was not different than placebo.

Treatment of Depression in the Menopausal Transition

While there is some evidence that estradiol may have a beneficial effect on depression, the effect is not robust or consistent. Treatment of depression in women can be tailored to address symptom profile, as well as stage of life in relation to their level of gonadal steroids, and stage in the menopausal transition. Traditional antidepressants are effective in the peri-menopausal period, although only few studies have specifically addressed this transition stage. One small trial by Ladd (n=16) assessed the effect of venlafaxine on both vasomotor and depressive symptoms in perimenopausal women (48). Several other studies demonstrated the efficacy of antidepressants for depression in the menopausal transition, including studies of citalopram and lexapro as monotherapy, and studies of remeron and celexa given in combination with HRT (49). Cohen reviewed the evidence for delineating subpopulations of women more or less responsive to different classes of antidepressant agents, and the findings are as yet inconclusive, with SSRIs and SNRIs (serotonin norepinephrine reuptake inhibitors) both appearing to be good options (49).

Parry compared groups of depressed peri- and postmenopausal women aged 45–72 receiving

SSRI alone, HRT alone or the combination. The outcomes measures were mood, cognition, and neuroendocrine changes, and the findings did not demonstrate HRT enhancement of mood effects beyond that seen with treatment of SSRI alone (50).

Estrogen may have a role as an augmenting agent in treatment-resistant depression or when first-episode depression occurs in the menopausal transition. SSRI may be the first line of treatment, but short-term use of estrogen may provide added benefit, especially for those women with hot flashes and other physical symptoms of menopause.

There is considerable interest in the use of alternative and complementary medicine therapies, particularly among women during the menopausal transition. There is a need for critical evaluation of botanical supplements used in perimenopause to determine both safety and efficacy for menopausal as well as for affective symptoms. Uebelhack investigated the efficacy of a combination of black cohosh and St. John's wort in a 16-week randomized, double-blind placebo-controlled trial and found it superior to placebo in reducing the menopause rating score as well as the HAM-D score (51). This promising approach requires further research.

Menopause and Anxiety

Some studies have looked at the prevalence of anxiety symptoms during menopause. This task is complicated because anxiety symptoms are often comorbid with depression. However, anxiety disorders are very common, and the National Comorbidity Survey, as quoted by Freeman, revealed a 17% prevalence of anxiety disorders with greater prevalence in women (22.6% vs. 11.8%) (52).

As in depression, women have twice the risk of anxiety disorders as do men. However, while it appears that the female susceptibility to depression is limited to the reproductive years, with the gender differences disappearing in midlife, it is not clear if anxiety symptoms also are mitigated at this point. Anxiety is one of the often-quoted symptoms of menopause, and in this context it is measured as a component of QOL scales and menopausal questionnaires in the research.

Almeida preformed a cross-sectional study of 265 older post-menopausal women, mean age 74.6 years. He examined the possible relationship of mood, anxiety and cognitive factors to serum estrogen levels (53). Depression, anxiety and QOL measures were correlated with serum estradiol and estrone levels. Low levels of these hormones were associated with greater depressive and anxiety symptoms, with a majority of significant findings evident with the estrone levels. Of note, the only other nonhormonal clinical characteristic differentiating the symptom group was the BMI, suggesting to the authors that among other unmeasured factors, physical fitness might be associated with mood (53).

The possibility that anxiety symptoms are less prevalent in post-menopausal years is suggested by a study by Bebbington in the U.K. (54). This investigator looked at the prevalence of depression, and mixed anxiety and depression International Statistical Classification of Diseases, 10th Revision (ICD-10) diagnosis in the National Survey of Psychiatric Morbidity in the British population, which included 9,792 households. His results showed a decrease in anxiety symptoms in women over age 55. Diagnosis was made by the Clinical Interview Schedule, Revised (CIS-R) clinical instrument. In women over 55, 1.1% had depression and 5.2% had mixed anxiety/depression while women under 55 years of age had nearly three times the prevalence of depression, and twice the prevalence of mixed anxiety (2.7% and 10.8%). Interestingly, the prevalence of both diagnostic categories increased for men as they reached 55 years of age, with depression prevalence of 1.7% vs. 5.3% in younger cohorts, and mixed anxiety/depression of 2.0 vs. 6.4% in younger cohorts. These differences remained after control for important social variables, including marital status, childcare, and employment status (54).

In a six-year population based-study using data from the Penn Ovarian Aging Study that followed 238 women (50% white, 50% African American), starting ages 35–47 who were premenopausal and were not taking any psychiatric drug or HRT (55). Anxiety was measured with the Zung Anxiety Index, a 20-item self-report scale. The findings were that anxiety is strongly associated with hot flashes even after adjusting for menopause stage, smoking, depressive symptoms, BMI, race, age, time and estradiol levels. In fact, anxiety preceded hot flashes in this cohort. Of note, in this study, African American women were 60% more likely than Caucasians to suffer from hot flashes. Depression was noted in about 1/3 of the overall sample and it increased in the early transition to menopause. In the multivariate model, the association of depressive symptoms to hot flashes was not observed (55).

Bipolar Disorder and Schizophrenia during Menopause

Other psychiatric syndromes have been associated with menopause. In women with pre-existing bipolar disorder, an increased risk of mood episodes during periods of hormonal fluctuation has been shown (32). A small study of 22 women found that estrogen may aid with mood stabilization (32).

It has been suggested that menopause may also be a risk factor for schizophrenia, since it has been observed that nearly 37% of female schizophrenics develop their illness after age 45 and a second peak in incidence (age 45–54 years) overlaps with the menopausal transition and this late onset schizophrenia. And there is often with a predominance of positive symptoms such as hallucinations and delusions. This pattern is distinct from that of males, in whom the development of schizophrenia is usually observed in the mid-twenties. Evidence of protective effects of estrogen is suggest by naturalistic studies in reproductive age female schizophrenia patients, finding that psychopathology scores drop when serum estradiol levels rise (56–58). Based on such findings, therapeutic interventions utilizing hormone replacement have been considered, although primarily as an adjunctive treatment.

Conclusion

Interest in women's health has included attention to cognitive and psychiatric issues. Hormonal transition is associated with an exacerbation of cognitive and affective complaints. It has been difficult to tease out the degree to which hormonal fluctuation is causative in these problems and the degree to which hormone replacement can mitigate such symptoms. Clearly the evaluation of cognitive and psychiatric symptoms should include a history and status of hormonal stage and expectations for symptom relief, and treatment should take into consideration whether hormonal status is in transition such as in he perimenopause or if it is in a steady-state such as post menopause. The use of hormone replacement to treat cognitive or affective symptoms is not clearly supported by the empirical data. However, when these symptoms are accompanied by menopausal symptoms, including hot flashes, estrogen is clearly indicated and may permit the observation of maximal benefit from other therapies.

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The Evaluation and Management of the Acutely Agitated Elderly Patient

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Abstract

Delirium is an organic mental syndrome defined by a global disturbance in consciousness and cognition, which develops abruptly and often fluctuates over the course of the day. It is precipitated by medical illness, substance intoxication/withdrawal or medication effect.

Delirium is associated with significant morbidity and mortality, and is a leading presenting symptom of illness in the elderly. Elderly patients with altered mental status, including agitation, should be presumed to have delirium until proven otherwise. The clinical manifestations of delirium are highly variable. A mental status evaluation is crucial in the diagnosis of delirium.

Medical evaluation and stabilization should occur in parallel. Life-threatening etiologies including hypoxia, hypoglycemia and hypotension require immediate intervention. The differential diagnosis of etiologies of delirium is extensive. Patients with delirium need thorough evaluations to determine the underlying causes of the delirium. Pharmacological agents should be considered when agitated patient has the potential to harm themselves or others, or is impeding medical evaluation and management. Unfortunately, the evidence to guide pharmacologic management of acute agitation in the elderly is limited. Current pharmacologic options include the typical and atypical antipsychotic agents and the benzodiazepines. These therapeutic options are reviewed in detail.

Key Words: Delirium, geriatrics, agitation, antipsychotics, benzodiazepines.

Introduction

THE AGITATED ELDERLY PATIENT poses a unique clinical challenge. Delirium represents a leading presenting symptomatology in acutely ill elderly patients. Agitation in the elderly should be presumed to be a manifestation of delirium until proven otherwise. When mental status changes present as agitation, the clinician is faced with a particularly difficult and complex scenario. A potentially immediately life-threatening etiology must be searched for and addressed. If agitation is severe, it requires urgent intervention to reduce potential danger to both patient and staff. Managing the agitated geriatric patient requires a coordinated approach that allows the staff to gain control of the situation while facilitating the diagnostic work-up. This article will provide a framework to use when evaluating the agitated elderly patient, including a review of available pharmacologic treatment.

Epidemiology

The population is becoming proportionately more elderly. The number of people over the age of 65 will double in the United States in the next 30 years (1). As the population ages, the elderly comprise a higher proportion of patients overall. This is especially true in the emergency department (ED). Persons age 65 and older account for 17.5 million ED visits in the U.S. annually and 15.4% of total ED visits (2). In a multicenter study, patients over age 65 accounted for 43% of hospital admissions from the ED (3).

The emergency department and acute hospital wards have the highest rates of patients presenting with delirium. Agitation in younger patients presenting to the ED are much more likely to be the result of substance abuse or underlying psychiatric disease (psychotic or mood disorder), than in the elderly population.

Delirium or mental status change is a leading presenting symptom for acutely ill elderly persons. In ED patients over 70 years old, it has been reported that up to 40% have an alteration in mental status, with approximately 25% diagnosed as having delirium (4). Levkoff et al. found that 24% of elderly patients from the community and 64% of those presenting from nursing homes were delirious upon hospital admission (5).

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Delirium is a medical emergency requiring prompt evaluation and treatment. It is generally reversible if the underlying cause is discovered and addressed, and can be fatal if overlooked and untreated. Hospital mortality rates in patients with delirium ranges from 25–33%. Elderly patients who develop delirium during hospitalization have a 22–76% chance of dying during that hospitalization. Hospital mortality is very high in patients that develop delirium—it is as high as the mortality rate associated with acute myocardial infarction or sepsis (6–8).

Delirium: Definition and Diagnosis

Delirium is an organic mental syndrome defined by a global disturbance in consciousness and cognition. It is characterized by a global cognitive impairment due to a medical condition, which develops abruptly and often fluctuates over the course of the day (9). The underlying mechanism of delirium is poorly understood and its pathophysiology has not been well elucidated. Delirium is common among medically compromised patients and the elderly are highly vulnerable to its development.

Hallmarks of delirium include disturbance in attention and memory impairment. Deficits in attention are characterized by ease of distractibility, with a reduced ability to focus, sustain or shift attention, resulting in difficulty in following commands. Patients may have trouble maintaining conversations, and conversations may be rambling or incoherent. Memory impairment usually involves recent memory; patients may be disoriented to time or place but only rarely to person. Perceptual disturbances that may occur include misinterpretations, illusions, or hallucinations. Often there are alterations in the patient's sleep/wake cycle. A fluctuating course is characteristic and lucid intervals may be misleading (Table 1).

The clinical manifestations of delirium are highly variable. Patients with delirium may present subtly or dramatically. If subtle, delirium may go unrecognized without formal mental status evaluation. Patients may present with psychomotor retardation with varying degrees of lethargy, withdrawal and somnolence. Alternatively, delirium may present dramatically with disruptive psychomotor agitation, emotional lability and hallucinations. In the elderly, delirium presents as agitation in less than one-third of cases (10).

TABLE 1
Key Features of Delirium

Altered level of consciousness ranging from stupor to agitation
Inattention, decreased ability to focus
Fluctuating course over hours or days
Often associated with sleep/wake cycle disturbance
Precipitated by medical illness, substance intoxication/withdrawal or medication effect
Leading presenting symptom of illness in the elderly
Life-threatening etiologies require immediate intervention
Underlying medical etiology must be determined and treated
Presume that altered mental status is delirium until proven otherwise

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Dementia

Patients with dementia are at risk for the development of delirium. Additionally, behavioral disturbances, including agitation, are common among patients with dementia. Agitation in dementia may include aggression, combativeness, delusions or hallucinations. Agitation may develop either as part of the clinical course or as a response to a new illness. An etiology for the agitation in patients with dementia must be sought, as agitation can be precipitated by pain and acute illness. When confronted with a confused elderly patient in the ED or hospital ward, it may not be apparent if the confused state is acute, subacute or chronic. It may not be possible to immediately distinguish between delirium and dementia, or determine which patients are suffering from both.

Mental Status Evaluation

A mental status evaluation is crucial in the diagnosis of delirium. Disorientation to the environment begins with the inability to identify the date, progresses to day of week, time, month, and year, and eventually to place. Only in the most severe cases is the person unable to identify self. However, if the mental status exam is limited to orientation to person, place and time, subtle cases of delirium may be missed.

The Mini-Mental Status Examination (MMSE) is an easy and reliable test that can be administered at the bedside. The MMSE is used to test for cognition, which includes orientation, registration (storing new information so that is can be retrieved later), attention and calculation, recall, visual-spatial ability and language. A high score on the exam makes a cognitive deficit unlikely, however, a low score is nonspecific and not diagnostic of any specific disorder. For hospitalized patients it has a sensitivity of 87% and specificity of 82% in detecting organic brain syndrome. Note that the MMSE must be interpreted with care in delirium since the delirious patient has impairment with attention, which interferes with exam performance (11, 12).

The Confusion Assessment Method (CAM) has been developed as an easy to use, sensitive, specific, and reliable diagnostic tool for the rapid detection of delirium (13; Table 2). It has a sensitivity of 93 – 100% and specificity of 90 – 95% for the diagnosis of delirium. This tool has four key features (acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness) used for screening for delirium. The first two features and one of the last two must be present to make the diagnosis of delirium.

Differential Diagnosis and Assessment

The differential diagnosis of etiologies of delirium is extensive (Table 3). Delirium is caused by a medical condition, substance intoxication or withdrawal, or medication side effect. It is an occult manifestation of systemic illness. In delirium, the underlying etiology must be treated in order to attain resolution as soon as possible. Initially information may be lacking and the etiology of the delirium may not be readily apparent. It is important to remember that a potentially life-threatening situation exists and that prompt intervention can be life saving. Therapeutic interventions may be required even before a specific underlying etiology is identified. Medical evaluation and stabilization should occur in parallel. Examples of immediately life-threatening causes include hypoxia, hypoglycemia, hypotension, acute myocardial infarction, and sepsis.

Common causes of delirium include infections, insufficiency of any major organ, medication or substance use or withdrawal, electrolyte or metabolic derangements and dehydration.

TABLE 2

Confusion Assessment Method (CAM) Diagnostic Tool

1. Acute onset and fluctuating course
2. Inattention, distractibility
3. Disorganized thinking, illogical or unclear ideas
4. Alteration in consciousness

The diagnosis of delirium requires the presence of both features 1 AND 2, plus EITHER feature 3 or 4.

Adapted with permission from Inouye S, van Dyck C, Alessi C, et al. Clarifying confusion: the confusion assessment method. Ann Intern Med 1990; 113:941 (13).

TABLE 3

Differential Diagnosis of Etiologies of Delirium

Hypoxemia
Hypercarbia
Hypoglycemia and hyperglycemia
Dehydration
Electrolyte disturbance (sodium, calcium, magnesium, phosphorus)
Infection (pneumonia, urinary tract)
Sepsis
Hypotension and hypoperfusion
CNS lesion, injury, infection (CVA, subdural hematoma, meningitis, encephalitis)
Endocrinopathies (thyroid, adrenal)
Acute abdominal pathology (diverticulitis, appendicitis, mesenteric ischemia, volvulus)
Renal failure
Hepatic failure
Cardiac disease (myocardial infarction, congestive heart failure, arrhythmia)

CNS = central nervous system; CVA = cerebrovascular accident.

History

A detailed medical history is important in elucidating the etiology of delirium. It is important to obtain information from as many sources as possible including the patient, emergency medical service providers, witnesses, family, caregivers and primary care providers. Information regarding the patient's baseline mental status and level of functioning should be ascertained. It is helpful to know if the patient has underlying dementia, if there has been an acute change and what underlying medical conditions exist. A very thorough review of medication use is important, as medications are very common precipitants of delirium in the elderly (14). The history should focus on causal factors related to the acute presentation such as history of trauma or fall, lack of oral intake, presence of systemic disease including metabolic and cardiopulmonary disorders, symptoms of infection, and substance use or withdrawal (15).

Physical Examination

Vital signs should be carefully reviewed and an accurate temperature and oxygen saturation measurement obtained. A bedside glucose determination is often considered the "fifth vital sign" and is particularly important in the evaluation of the agitated patient (16). A meticulous physical examination must be performed, including neurologic and mental status examination (see mental status evaluation above). The examination should search for evidence of medical or surgical causes for the patient's condition, including trauma, infections and focal neurologic deficits.

Diagnostic Testing

Delirium requires an extensive evaluation that is further directed by clinical suspicion and response to interventions (Table 4). Laboratory eval-

TABLE 4

Assessment of the Patient with Delirium

Vital signs including accurate temperature measurement
Physical examination with thorough neurologic exam
Oxygen saturation
Stat glucose
Chemistry including electrolytes, renal function, liver function panels
Urinalysis
Chest x-ray
Electrocardiogram
Dependent upon the clinical scenario consider: head CT, lumbar puncture, blood cultures, toxicology screening, thyroid function

uation usually includes a complete blood count, electrolytes, glucose, renal and hepatic testing. A urinalysis and chest x-ray should be obtained to rule out infection. An electrocardiogram is indicated to evaluate for myocardial ischemia and arrhythmia, and to assess for QTc prolongation. Additional tests including toxicologic screens, serum levels (alcohol, aspirin, acetaminophen), and thyroid function tests may be indicated if a cause is not found on initial evaluation. A history of falls, suspected trauma, and focal findings on physical exam are indications for early neuroimaging (17). Neuroimaging should also be considered if no etiology for the delirium is identified after an initial evaluation is completed (18). Examination of the cerebrospinal fluid is needed when meningitis or encephalitis are suspected.

Risk Factors, Supportive Care and Non-pharmacologic Interventions

Delirium is a multifactorial disorder. The elderly are particularly vulnerable to the development of delirium. It is of paramount importance to try to prevent delirium before it occurs. Implementation of preventive interventions has been demonstrated to substantially reduce the risk of delirium in older hospitalized patients (19–21). Patients should be provided with an optimum level of sensory stimulation. Environmental cues and family members should be available to help re-orient patients. Patients are particularly vulnerable to the development of delirium if they are sleep deprived, dehydrated, immobilized, or have vision or hearing impairments. Patients who require hearing aids or eyeglasses should have them available to prevent sensory deprivation. Excess noise should be avoided whenever possible and patients should be allowed to have uninterrupted sleep. Oral fluids should be encouraged and if oral fluids are contraindicated, intravenous hydration should be provided. Physical restraints should be avoided, since they may increase agitation and are associated with injury and death (22).

The use of unnecessary medications should be avoided and required therapeutic agents should be selected with the most favorable side effect profile possible (14). However, pain is an important precipitant of delirium and it is important to provide adequate analgesia to patients suffering from pain (23–25).

Pharmacologic Management

Pharmacologic management is necessary in more severe cases of agitation in which patients are a danger to themselves or others, or are impeding medical evaluation and care. The ideal agent for undifferentiated acutely agitated geriatric patients would be effective with a rapid onset of action and would be safe with minimal side effects. Pharmacologic therapy in the elderly is complicated by altered concomitant age-related disorders and altered pharmacokinetics and pharmacodynamics. The elderly are more susceptible to drug toxicity in part due to decreased renal and hepatic function, as well as confounding polypharmacy. In general, drugs should be administered in the lowest effective dose.

Unfortunately, there is little evidence in the literature to guide the pharmacologic treatment of acute agitation in the elderly population. Most studies of the emergent sedation of acutely agitated patients are in a younger patient population and typically include substance abusers and patients with underlying psychiatric disturbances (e.g., psychotic or mood disorders), often without other concomitant medical problems. There are several studies that evaluate the long-term management of chronic agitation but not acute agitation in the demented elderly.

Pharmacologic options include the benzodiazepines and the typical and atypical antipsychotics agents. These options are discussed in the following sections. For rapid sedation of an acutely psychotic patient the intravenous (IV) route is preferred. In situations where establishing an IV is difficult or hazardous because of the patients agitation, the intramuscular (IM) route may be necessary. In general, oral sedation has little role in the uncooperative acutely agitated patient in an emergency setting. However, an oral agent may be considered if symptoms of agitation are not severe and may be considered prior to the escalation of symptoms.

Typical (First-Generation) Antipsychotics

Typical or conventional antipsychotics block dopamine D-2 receptors in the brain. The mechanism by which they reduce agitation has not been elucidated, even though they are used extensively for this purpose. Typical antipsychotics are grouped into high, mid and low potency agents. High-potency typical antipsychotics include the butyrophenones (haloperidol) and droperidol. Low-potency typical antipsychotics include the phenothiazines (chlorpromazine), and thioridazine. Typical antipsychotics are associated with extrapyramidal symptoms (including rigidity, dystonia, bradykinesia, tremor, akathisia, and tardive dyskinesia) and anticholinergic side effects (including dry mouth, urinary retention and decreased cognitive function). Caution should be used in treating patients suffering from Parkinson's disease with typical antipsychotics because of the significant risk of worsening of the extrapyramidal features of the disease. A rare side effect of antipsychotic medication is the neuroleptic malignant syndrome, which is manifested by high fever, rigidity, mental status changes and autonomic instability. Patients on long-term antipsychotic therapy are at cumulative risk for the development of tardive dyskinesia, which is characterized by involuntary choreoathetoid movements. Low-potency antipsychotics are associated with a high incidence of anticholinergic side effects that can worsen cognitive function. They are much more sedating due to their antihistaminergic effects, and their alpha-adrenergic blocking effects may lower blood pressure. The side effect profile of the low-potency agents renders them inappropriate for use in the elderly.

Haloperidol is commonly used for the treatment of agitation because of its lower incidence of respiratory depression, hypotension and anticholinergic effects. Haloperidol is not Food and Drug Administration (FDA) approved for IV use, although it is commonly administered by this route and thought to be safe. Numerous studies have demonstrated its efficacy in treating aggression; however, most of these studies were of younger patients with a known psychiatric disorder (26). In 1999, the American Psychiatric Association published a practice guideline that recommended haloperidol as a drug of choice for managing the patient with delirium (27). Although there is substantial evidence of haloperidol's efficacy and safety in controlling acute agitation, published studies have included few if any elderly patients. In a study by Clinton et al., haloperidol was demonstrated to be safe and effective for the sedation of disruptive ED patients in a study in which the mean patient age was only 33 years (28). In a randomized, double-blind study of hospitalized AIDS patients with delirium, either haloperidol or chlorpromazine was found superior to lorazepam in controlling symptoms (29).

The efficacy and safety of haloperidol in the management of chronic behavioral symptoms in the demented elderly has been evaluated. A Cochrane Systematic Review of five randomized, placebo-controlled trials showed that demented subjects receiving haloperidol exhibited no significant improvement in overall agitation scores when compared to those treated with a placebo, but did find that aggression, one subtype of agitation, decreased in the haloperidol group when compared to controls (30). Unfortunately, in these studies outcomes were measured no earlier than 3 weeks after initiation of treatment. Patients receiving haloperidol reported more adverse reactions but there was no significant difference in the dropout rate from the studies between haloperidol-treated subjects and placebo controls.

Droperidol is more potent and more sedating, and has a more rapid onset and a shorter half-life than haloperidol. IM droperidol has been demonstrated to have more rapid onset and greater efficacy than IM haloperidol alone for patients with acute psychosis (31, 32). Droperidol has been used effectively for the rapid tranquilization of acutely agitated and violent patients in the ED (33). A retrospective review of its use and safety in 2,500 emergency department patients, including 141 patients over the age of 66, found that despite its widespread use, complications were extremely rare (34). In 2001, the FDA required a boxed warning for droperidol because of reports of death associated with QTc prolongation and development of torsades de pointes. There is controversy in the literature regarding the boxed warning issued to droperidol, given the decades of successful clinical use (35, 36). There is evidence to suggest that haldol is also associated with QTc prolongation and torsades de pointes (37–39).

Atypical (Second-Generation) Antipsychotics

Atypical antipsychotics act at both serotonin and dopamine receptors, and have been approved by the FDA for the treatment of schizophrenia. However, they have not been approved for the treatment of behavioral disorders in patients with dementia. In recent years numerous agents have been developed, with the anticipation of an improved side effect profile compared with typical or first-generation antipsychotics. Atypicals have been marketed as having safety profile with fewer side effects of akathisia, parkinsonism, tardive dyskinesia, sedation, peripheral and central anticholinergic effects, postural hypotension and cardiac conduction defects. A recent FDA advisory with a mandatory boxed warning on manufacturers labeling calls this into question (40, 41). The FDA determined that the treatment of behavioral disorders in elderly patients with dementia with atypical (second generation) antipsychotic medications is associated with increased mortality. Analyses of 17 placebo-controlled studies with enrollment of 5,106 patients receiving four different drugs (olanzapine, aripiprazole, risperidone, and quetiapine) had a death rate 1.6–1.7 times higher than with placebo. Therefore, the FDA concluded that the effect is probably related to the common pharmacologic effects of all atypical antipsychotic medications, including those that have not been studied in the dementia population. Over the course of these trials, averaging 10 weeks in duration, the death rate in the treated groups were 4.5% compared to the rate of 2.6% in the placebo groups. Varied causes of death, most were either cardiovascular or infectious (e.g., congestive heart failure, sudden death, pneumonia). However, the FDA has considered adding a similar warning to the labeling for typical antipsychotic medications because the limited data suggest a similar increase in mortality for these drugs. Additionally, the recently published Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), which compared the effectiveness of atypical antipsychotic agents with that of older agents in patients with chronic schizophrenia, also sheds doubt on the advantage of atypical agents over typical antipsychotics (42). This study found no statistically significant difference in efficacy or the incidence of extrapyramidal side effects.

Despite the FDA warnings, there is significant literature to support the use of these agents in the management of agitation in dementia. Just prior to the FDA warning bulletin, *The Expert Consensus Guideline Series. Treatment of Dementia and Its Behavioral Disturbances* recommended the use of atypical antipsychotics over conventional antipsychotics (43).

Olanzapine have been shown to be effective in the treatment of chronic agitation in the elderly patient. Most studies have focused on the management of behavioral disturbances in nursing home patients over the course of days to weeks and not on the treatment of acute agitation (44–46). There is some data to support the use of olanzapine in the management of acute agitation in the elderly. IM olanzapine was compared to haloperidol and lorazepam in the treatment of acute agitation in the ED for patients with schizophrenia and bipolar disorders (>18 years of age) and dementia (>55 years of age) (47). In the dementia group agitation was significantly reduced by olanzapine (2.5 mg) when compared with placebo, with no more sedation than lorazepam (1 mg). Olanzapine was not compared to haloperidol in the dementia group. Meehan et al. (48) compared the efficacy and safety of rapid-acting IM olanzapine in treating agitation associated with Alzheimer's disease and vascular dementia. In this double-blind study, 272 acutely agitated patients were randomized to treatment with olanzapine (dosages of 2.5 and 5.0 mg), lorazepam (1.0 mg), or placebo. At 2 hours, both olanzapine (2.5 and 5 mg) and lorazepam showed superiority over placebo in terms of reduced agitation. At 24 hours both olanzapine groups maintained superiority over placebo; lorazepam did not. There were no significant differences in sedation, adverse events, extrapyramidal symptoms, QT interval, or vital signs among all groups. Currently data supporting the use of olanzapine for acute agitation in the elderly are limited.

Ziprasidone is available in an IM formulation. In double-blind, randomized study in a younger population (79 subjects, age 20–62 years of age), ziprasidone was shown to be effective in reducing acute agitation associated with psychosis, with an excellent side effect profile (49). A retrospective study of the safety of IM ziprasidone in agitated elderly patients admitted to a neuropsychiatric service found no significant differences in QTc intervals of treated patients (50). A case series of 5 patients with Parkinson's disease demonstrated no deterioration of motor function or other relevant side effects in patients treated with IM ziprasidone for acute agitation (51). Data are limited to support or refute the use of ziprasidone for acutely agitated elderly patients.

Risperidone has been extensively studied for the management of psychosis and behavioral disturbances in patients with dementia. The only currently available parenteral formulation is an extended-acting, slow-release formulation that is dosed bi-weekly and therefore not suitable for use in acute agitation. However, there is an available rapidly dissolving oral tablet. A number of studies have demonstrated its efficacy and safety for the longer-term management of agitation in the elderly (52–54). There is one study suggesting the efficacy of risperidone in controlling the agitation of delirium over several days (55). In this retrospective review, 41 subjects received risperidone and 36 received haloperidol, with both agents demonstrating effectiveness. However, the use of risperidone to immediately control acute agitation has not been studied.

Benzodiazepines

Benzodiazepines potentiate the effect of gamma amino butyric acid (GABA) by binding to GABA receptors in the brain. Benzodiazepines are effective and commonly used to sedate violent and severely agitated younger patients. In younger patients benzodiazepines produce a rapid decrease in agitation with minimal side effects. However, they are respiratory depressants and respiratory status must be closely monitored after administration. There are few data in the literature regarding the use of benzodiazepines for the control of acute agitation in the elderly.

Diazepam has no role in the treatment of the elderly because of its prolonged half-life and active metabolites. Midazolam has the fastest onset of action and the shortest duration of effect.

In a study by Nobay et al. in younger patients (mean age 40.7), IM midazolam had significantly shorter onset of action and shorter duration of effect than both IM haloperidol and IM lorazepam (56). In a study by Martel et al. of acute undifferentiated agitation in patients with a mean age of 37 years (range 19–68), 5 mg of IM midazolam achieved adequate sedation more rapidly than 5 mg of droperidol or 20 mg of ziprasidone (57). Respiratory depression requiring supplemental oxygen administration was a frequent adverse effect.

Intramuscular lorazepam has been widely studied for sedation of the agitated young patient in the ED (56–59). However, only one randomized, controlled trial investigated its use in the delirious elderly patient (48). In this study, lorazepam was more effective than placebo in reducing agitation and was well tolerated. The risk of respiratory depression was not specifically assessed.

There are many recommendations in the literature advising against the use of benzodiazepines in the elderly. Elderly demented patients with chronic agitation treated with benzodiazepines are at an increased risk of falls, sedation and cognitive impairment (60–62). However, these adverse effects are probably not relevant to the acute temporary management of an agitated patient.

There is a body of evidence regarding safety and efficacy information of benzodiazepines in elderly patients undergoing conscious sedation for elective procedures or receiving them as pre-anesthetic adjuncts. Randomized trials do not reveal a significant risk of post-sedation cognitive impairment in elderly patients receiving intravenous midazolam for conscious sedation (63, 64). Clinical trials have identified a risk of hypoxia and respiratory depression with IV administration of midazolam when given alone to the elderly (65). This risk may be higher in the elderly than in younger patients (66). There may be an increased risk of hypoxia in patients with underlying respiratory disease, such as chronic obstructive pulmonary disease, as well.

There is little data to support concerns of potential behavioral disinhibition or paradoxical agitation in response to benzodiazepine administration in the elderly. The literature is generally limited to case series (67, 68), and there is no strong evidence that the elderly are at any increased risk of this adverse effect.

There are several clinical scenarios in which benzodiazepines offer an advantage over antipsychotics. Benzodiazepines are the treatment of choice for delirium related to alcohol or benzodiazepine withdrawal (27). Benzodiazepines are particularly effective in agitated patients with sympathomimetic toxidromes, such as in cocaine and phencyclidine intoxication (33). Since benzodiazepines are not associated with extrapyramidal symptoms, they are not contraindicated in patients with Parkinson's disease. Benzodiazepines may be the preferred sedative in situations where raising the seizure threshold is important.

Combination Therapy

The combination of an antipsychotic and a benzodiazepine is often used for the rapid tranquilization of acutely agitated, violent younger patients. A study of haloperidol and lorazepam in patients with an average age of only 34.2 years demonstrated that the combination of the two was more effective than either drug alone (59). However, the American Psychiatric Association's Practice Guideline for the treatment of delirium cited combination therapy with a typical antipsychotic and a benzodiazepine as potentially beneficial in that it allows for the use of a lower dose of each medication and thus lowers the risk of each drug's side effects (27). The treatment of elderly agitated patients with a combination drug therapy has not been studied. In general it is thought to be best to minimize the number of medications when treating geriatric patients.

Summary

The hallmarks of delirium include global cognitive impairment, relatively rapid onset of symptoms, and a fluctuating clinical course over a period of hours to days. The elderly are particularly susceptible to delirium. Delirium is associated with significant morbidity and mortality. Elderly patients with acute mental status changes including agitation should be assumed to be suffering from an acute medical illness until proven otherwise. More subtle cases of delirium may not be recognized if an accurate mental status examination is not performed. Delirium is a medical emergency due to the multiple possible serious underlying medical causes. There is a need to provide immediate interventions for urgent medical conditions. Medical evaluation and stabilization should occur in parallel. Virtually any medical condition can precipitate the development of delirium. Patients with delirium need thorough

TABLE 5

Summary of the Initial Evaluation and Management of the Agitated Elderly Patient

Provide immediate interventions for urgent medical conditions
Assume the etiology of the agitation is delirium
Assess for underlying etiology or exacerbating factors and manage appropriately
Review history of present illness, medical history and medication profile
Provide optimal environmental and supportive interventions
Pharmacological agents should be considered when the patient has the potential to harm themselves or others, or is impeding medical evaluation and management
Pharmacolo]ents must be used in age-adjusted doses

work-ups to evaluate for the underlying cause of the delirium.

Rapid sedation is necessary if the patient is a danger to self or others, or if the agitation is impeding medical evaluation and management. Unfortunately, the evidence to guide pharmacologic management of acute agitation in the elderly is limited. Current pharmacologic options include the typical and atypical antipsychotic agents and the benzodiazepines. There are FDA boxed warnings of increased mortality for the use of droperidol and the atypical antipsychotics, rendering their use problematic. Haloperidol appears to be generally safe and effective and causes less respiratory depression than the benzodiazepines. However, the benzodiazepines may be preferable in particular clinical scenarios. It is important to remember to reduce dosing in elderly patients as they have altered pharmacodynamics and pharmacokinetics (Table 5).

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Dementia:

A Brief Review

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Abstract

Dementia is an increasingly common diagnosis in our aging population, and the numbers are expected to rise exponentially in coming years. Alzheimer's disease alone now affects 4.5 million people in the US, while millions more are currently affected by vascular dementia, Lewy Body disease and frontotemporal dementia. Each of these is a distinct entity, though overlapping symptoms and comorbidities occur frequently. Within the past two decades research has progressed rapidly on multiple fronts, including epidemiology, etiology, pathology, diagnosis and treatment. It is important for clinicians to recognize early signs and symptoms of dementia, and to note critical differences among them. Dementia research has moved beyond description of symptoms and clinicopathological correlation to the elucidation of risk factors, the pathobiology of the disease process, and most important, to the first generation of dementia treatments. Our purpose here is to review the current state of knowledge and directions of research for the four major dementias noted above. We are entering an era of dementia care that will be based upon the identification of potentially modifiable risk factors and early disease markers, and the application of new disease-specific diagnostic tools and treatment modalities.

Key Words: Aging, dementia, diagnosis, treatment, pathology, Alzheimer's disease, vascular dementia, Lewy Body disease, frontotemporal dementia.

Introduction

THE CLINICAL PICTURE OF DEMENTIA as a deterioration in cognition in later years has been recognized for centuries but understood in its current formulation only for the past three decades. In the late 19th and early 20th centuries the shift in the conceptualization of mental illness away from moral causation towards disease etiologies extended to dementia, which was then conceived as an effect of aging and related to arteriosclerosis. Alzheimer's disease (AD) did not emerge as a distinct disease until the mid-20th century, which led to the recognition of multiple diseases of cognition with different etiologies.

The dementias can be categorized according to clinical presentation, neuropathology and/or etiology. Research criteria have defined four major dementia groupings: Alzheimer's dementia; the Parkinson's group (including Lewy Body disease, dementia of Parkinson's and Alzheimer's dementia with Parkinson's); the frontotemporal group (including Pick's disease and Semantic dementia); and the vascular group (including large and small vessel disease). This review will focus on these four major categories of dementia.

Alzheimer's Disease

AD is the most common type of dementia in this country in clinical and autopsy surveys. Plaques and tangles had been observed by others prior to Alzheimer's investigations in the early 20th century. What intrigued Alzheimer about his original case, Auguste D. was the clinical presentation of paranoid delusions, and marked and progressive cognitive deterioration in a young patient (in her 50s) coupled with unusual pathological findings of "a clotting of fibrils….in addition an extraordinary number of peculiar patches disseminated throughout the entire cortex." In the following decades efforts were focused on determining the biochemical composition of the plaques and tangles, their specificity and their correlation with the clinical picture. The advent of electron mi-

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croscopy in the 1960s ultimately revealed that amyloid, a substance familiar to pathologists since the 19th century, formed the central core of the plaque and that the tangles were neurofilaments.

Epidemiology

The current prevalence of AD in the U.S. is estimated at 4.5 million, a number expected to rise threefold over the next 50 years as the population ages (1). Age is the strongest risk factor for AD. In Rochester, Minnesota the incidence of new AD cases between 1960 and 1975 was 66/100,000 per year at age 60–69, 409/100,000 per year at age 70–79, and 1,479/100,000 per year age 80 and older (2).

Risk Factors

In large population studies lower education has repeatedly been identified as a risk factor for the development of AD, while higher education correlates with older age at onset and possibly with lower overall risk (3). This pattern has been attributed to brain and cognitive reserve. Gender, marital status and living in an urban area have been suggested as possible risk factors for Alzheimer's, though further studies are needed.

There are three so-called "Alzheimer genes," autosomal dominant genes responsible for many familial cases of AD: Presenilin I, Presenilin II, and APP, which are thought to work through increased production of Aβ peptides. These genes are relatively rare, accounting for only 5% of cases, usually the early-onset variant. Most AD cases, particularly with onset after the age of 65, are "sporadic," i.e., occur in the absence of one of the causative genes and without an identified family history. The major susceptibility gene associated with sporadic late-onset AD cases is apolipoprotein e4 (APOe4). By age 85 those homozygous for the APOe4 allele (2% of the population) have a 50–90% chance of developing AD, and those heterozygous for the APOe4 allele (15% of the population) have a 45% chance, in contrast to the 20% chance in the general population (4).

Lifestyle, too, appears to play a role. Patients with more and more varied activities, including intellectual, physical, recreational and social activities, are less likely to develop AD (5). Social network size seems to modify the effect of brain pathology on cognition, as suggested in one clinicopathological study in which cognitive function remained higher for subjects with larger social networks (6). Medical risk factors for AD include head trauma as remote as several decades prior to onset of dementia, diabetes mellitus and clinical depression (7–9).

Pathobiology/Etiology

AD at the outset was identified by its unique pathology, the plaques and tangles that Alzheimer referred to as "a clotting of fibrils.... in addition an extraordinary number of peculiar patches disseminated throughout the entire cortex." These pathological findings have driven the etiologic search through the identification of the biochemical and ultrastructural composition of the plaques and tangles. Several theories of pathogenesis are in debate. The amyloid cascade hypothesis (10), first articulated in 1992, is the dominant explanation for Alzheimer disease development. This hypothesis derives from what has been learned regarding plaque composition and AD pathogenesis over the past three decades. The fundamental abnormality is an excess of Aβ peptides brought about through either overproduction or diminished clearance. Patients with missense mutations in the APP, Presenilin 1 and Presenilin 2 genes are lifelong overproducers. It is postulated that late-life onset AD (aka "typical" or "sporadic" AD) results from a failure of metabolism and degradation rather than overproduction of Aβ. Secondary protective responses such as microglial activation, an inflammatory response and free radical formation are part of the toxic cascade induced by amyloid accumulation, which ultimately contributes to neuronal death, leading to the clinical manifestations of dementia.

Initially it was thought the plaque was necessary to initiate this toxic cascade, but it is now considered more likely that the Aβ monomers and oligomers initiate the process, long before organizing into plaques. These small molecules are thought to disrupt synaptic function even in apparently healthy neurons, accounting for the affected neurons' degeneration.

Signs and Symptoms

The clinical hallmark of Alzheimer's disease is memory impairment. A sense of memory failure, detected by the patient or a close relative, is usually the presenting symptom. Motor and sensory symptoms are absent until late in the course of the disease. However, other cognitive domains, such as language, praxis and recognition skills, are affected even early in the presentation.

Course

AD has a gradual and progressive course, typically 10 years from diagnosis to death. The advent of cholinesterase inhibitors has had some effect on the course of disease for individual subjects, though population trends have been harder to demonstrate (11, 12).

Diagnosis

The diagnosis of AD remains a clinical diagnosis. A history of insidious onset with subtle and gradual progression, the presence of characteristic symptoms such as problems with retaining recent information or struggles to come up with words are suggestive of AD. Neuropsychological testing demonstrating a pattern of lower than expected performance on memory tasks and (usually) language, often with more semantic than phonemic difficulties (meaning that the patient has more difficulty generating words in specific categories, such as animals, than in generating words that begin, for example, with the letter F) is particularly informative in the earliest stages. The neurological exam shows lack of focal findings. Examination of blood or cerebrospinal fluid (CSF) is typically normal, with no evidence to suggest another etiology. Genetic testing is not part of the diagnostic workup, since the most common susceptibility gene, APOe4, is not diagnostic. There are no biomarkers or imaging scans that are diagnostic or reliably predictive of who will develop AD. Imaging serves the clinical function of ruling out other etiologies that are visible on scan (e.g., stroke, tumor or rare dysgenesis). Structural imaging can provide evidence of atrophy, which is seen in virtually all cases of AD but is not specific to AD. Imaging of amyloid in live patients using radioactive ligands visualized on positron-emission tomography (PET) scan has been demonstrated at several sites. This has the potential to develop into a preclinical diagnostic marker, but is still in experimental stages.

CSF is not routinely obtained in the evaluation AD. There is a characteristic pattern of elevated CSF Aβ and hyperphosphorylated tau and total tau, but specificity is inadequate for this to serve as a diagnostic marker.

Treatment

A decade ago there was no treatment for Alzheimer's disease. Early treatment studies were predicated on the role of cholinergic neurotransmitters in memory function. Tacrine, the first cholinesterase inhibitor, introduced in 1992, proved too hepatotoxic for widespread use, but it did help create a paradigm shift for perceiving AD as a treatable disease. The first wave of Alzheimer's treatment that began with Tacrine was followed by three other cholinesterase inhibitors with better safety and tolerability profiles: donepezil, rivastigmine and galantamine. All of these agents were approved for the treatment of mild-to-moderate severity AD after demonstrating the ability to forestall decline for 6–12 months. In 2003, memantine, an *N*-methyl-D-asparate (NMDA) antagonist, was approved for the treatment of moderate severity AD. There are currently over 70 compounds in human trials, most targeting steps in the toxic amyloid cascade. These include interfering with Aβ aggregation, enhancing its metabolism, diminishing the production of toxic Aβ peptides and enhancing the enzymatic formation of non-soluble Aβ peptides. Other approaches interfere with tau hyperphosphorylation or target downstream responses to or byproducts of amyloid cascade: inflammation, oxidation and apoptosis.

In tandem with treatments, better measurement tools are being developed. Future treatment of AD will involve an assessment of risk factors and specific strategies aimed at ameliorating specific risks. Treatment efficacy will be monitored *in vivo* through amyloid imaging and serum/CSF biomarkers.

Vascular Dementia

Epidemiology

Vascular dementia is the second most common form of dementia after Alzheimer's disease among the elderly. Pooled prevalence from eight European countries was 1.6% for vascular dementia in subjects older than 65, compared to a prevalence of 4.4% for AD (13). A meta-analysis of the European studies on the incidence of dementia showed vascular dementia constituted 17.6% of all incident dementia (14).

Diagnosis

Vascular dementia may be the result of a single strategic infarct, multiple cortical or lacunar infarcts or a microvascular insult in which neither clinical symptoms of stroke nor infarcts by imaging are evident. Conversely, the mere presence of multiple (or strategic single) infarcts on imaging does not automatically imply vascular dementia. No specific pattern of cognitive deficits defines vascular dementia and neuropsychological testing cannot differentiate vascular dementia from Alzheimer's disease (15).

The impact of computed tomography (CT) and magnetic resonance imaging (MRI) on the diagnosis of vascular dementia is still undetermined. Number of infarcts, location, size and unilateral vs. bilateral distribution make quantification of lesions for the diagnosis of vascular dementia very difficult. A strategically placed infarct in the thalamus, caudate or hippocampus, however small, can cause marked cognitive decline. Some patients can be amazingly resilient despite having extensive infarcts on imaging: 20% of cognitively normal elderly had clinically silent lacunar infarctions on MRI (16). However, many such subjects had lower scores on neuropsychological testing and a higher risk of future dementia than their counterparts without lacunae (17).

Risk Factors

There is an elevated risk for subsequent dementia in patients who have had a stroke in comparison to controls without any evidence of a stroke (18). Diabetes and hypertension are stronger risk factors for vascular dementia than for Alzheimer's disease (19). The apolipoprotein e4 genotype is a risk factor for vascular dementia as well as AD (20).

Pathology

Dementia is a clinical syndrome that does not directly correlate with size, location or type of ischemic infarct. Microvascular pathology, including foci of pallor, neuronal loss and gliosis, has been found to play a causal role in dementia (21). Dementia was also found to be better correlated with the amount of hippocampal and cortical atrophy than with the volume of the lacunae (22). The role of microvascular ischemic changes in the white matter in cognitive decline is still an open question (23).

A British study found 11% of autopsied dementia cases had pure vascular dementia and another 20% had a combination of vascular dementia and AD (24). There is compelling evidence that vascular pathology and AD pathology are additive, and patients with a combination of both pathologies have a clinically more severe dementia.

Treatment

Cholinesterase inhibitors have been used successfully in patients diagnosed with vascular dementia (25). Galantamine and donepezil improved cognition in patients with probable and possible vascular dementia in comparison to placebo (26). Several clinical trials have shown that antihypertensive therapy prevents the onset of vascular dementia (27).

Dementia With Lewy Bodies

Dementia with Lewy bodies primarily affects the basal ganglia. Lewy bodies and Lewy neurites are pathologic aggregations of alpha-synuclein, a ubiquitously expressed synaptic protein that has been implicated in vesicle production (28). Lewy bodies also contain chaperone proteins and elements of the ubiquitin-proteasome system; however, these features are non-specific, in that they are also found in other neuronal inclusions, such as the neurofibrillary tangles found in AD. Immunohistochemical staining for alpha-synuclein has been shown to be the most sensitive and specific method for detecting Lewy bodies and can be used in a semiquantitative grading of severity of Lewy-related pathology (29).

Dementia with Lewy bodies is thought to be the third most common type of dementia in the elderly, accounting for 10 – 15% of cases at autopsy. In population-based studies of subjects aged 65 and older, the prevalence of dementia with Lewy bodies was found to be 0.7%, which is consistent with its rate of 10 – 15% of hospital-based cases at autopsy (30). The epidemiology of dementia with Lewy bodies is sparse; age and gender distribution and potential risk factors have yet to be defined.

Many patients with dementia with Lewy bodies also have Alzheimer's disease pathology, which alters the clinical presentation. Dementia with Lewy bodies' patients who also have many neurofibrillary tangles display more core clinical features of AD (31). Conversely, Lewy bodies also occur in more than half of all patients with sporadic and early-onset AD (32). The number of cortical Lewy bodies correlates only weakly with severity and duration of the dementia, whereas Lewy neurites are more closely linked with clinical symptoms (33).

Strong similarities have been found between dementia with Lewy bodies and Parkinson's disease dementia, both of which are clinically defined syndromes. The use of an arbitrary 1-year rule has been used to separate the disorders: onset of dementia within 12 months of parkinsonian symptoms qualifies as dementia with Lewy bodies; and dementia that begins more than 12 months after the onset of parkinsonian symptoms as Parkinson's disease dementia. However, there are no definite pathological criteria that distinguish the disorders.

Signs and Symptoms

The essential feature for a diagnosis of possible or probable dementia with Lewy bodies is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function.

Fluctuations (waxing and waning of cognition, functional abilities and arousal from almost normal to markedly confused or hypersomnolent) are a core feature of dementia with Lewy bodies. Another core feature is visual hallucinations that are usually vivid, colorful and well-formed false perceptions of animals or people. Visual illusions and delusions, which typically have a paranoid quality, are also common. Auditory, tactile or olfactory hallucinations are rare. Other common neuropsychiatric features include depression, apathy and anxiety. Agitation and aggressive behavior tend to occur late in the course of the illness, if at all. Spontaneous parkinsonism unrelated to dopamine antagonist exposure is also a core feature of dementia with Lewy bodies. Signs and symptoms include tremor, bradykinesia, rigidity, shuffling gait, masked facies, stooped posture and retropulsion. Rapid eye movement (REM) sleep behavior disorder is common in dementia with Lewy bodies, as well as in Parkinson's disease (34). Affected patients act out their dreams by screaming and kicking, which can cause injuries to themselves and their bed partners. The dreams often have a chasing or attacking theme, and their content tends to match the exhibited behavior. Interestingly, REM sleep behavior disorder often begins years to decades before any other cognitive or motor symptoms develop.

Imaging

Functional imaging of the dopamine transporter yields information on the integrity of the nigrostriatal dopaminergic system and is abnormal in dementia with Lewy bodies and Parkinson's disease, but is normal in Alzheimer's disease (35). Low dopamine transporter uptake in the basal ganglia by PET or single-photon emission-CT (SPECT) imaging is therefore a suggestive feature of dementia with Lewy bodies. Currently there are no specific findings for dementia with Lewy bodies on laboratory testing of blood or CSF.

Treatment

Several studies have shown improvement of cognitive functioning and neuropsychiatric symptoms with cholinesterase inhibitors (36, 37). Theoretically, cholinergic stimulation should worsen parkinsonism, but in practice use of cholinesterase inhibitors rarely causes an increase of parkinsonian symptoms. Cholinesterase inhibitors have been shown to also help improve visual hallucinations, but if they are not frightening to the patient, reassurance may be sufficient. Psychostimulants, levodopa/carbidopa and dopamine agonists have also been reported to improve cognition, apathy and psychomotor slowing. Management of fluctuations has been difficult.

Atypical neuroleptics like clozapine, quetiapine, risperidone or olanzapine have been slightly effective with delusions and agitation (38, 39). Depression and anxiety respond to selective serotonin reuptake inhibitors (SSRIs), and electroconvulsive therapy can be effective in some patients without affecting cognition. Many of the parkinsonian symptoms of dementia with Lewy bodies respond to levodopa/carbidopa and the dopamine agonists.

Clonazepam is the mainstay of therapy for REM sleep behavior disorder, with melatonin alone or as add-on therapy effective as well. Mirtazapine and trazodone may improve insomnia. Continuous positive airway pressure (CPAP) therapy can be tolerated well by dementia patients and sometimes significantly improves alertness and cognition.

Frontotemporal Dementia

Signs and Symptoms

Frontotemporal dementia (FTD), also known as Pick's disease, encompasses a diverse group of clinical and pathological disorders. There are several distinct clinical presentations, most commonly behavioral changes, but a language disorder, usually in form of a progressive non-fluent aphasia, can be the main presenting sign. The most common clinical presentation of FTD is characterized by profound changes in personality and social conduct, including a decline in manners and social skills that are incongruent with the patient's premorbid behavior. Active antisocial and disinhibited verbal, physical and sexual behavior (e.g., tactlessness, offensiveness, disinhibited speech and gestures, incontinence and sexual exposure) are usually present at the initial presentation of the patient. Affected patients lack emotional warmth, empathy and sympathy and are indifferent to others. There is usually a quantitative change in customary behavior ranging either from profound apathy, inertia or passivity to overactivity or increased talking, laughing, singing, sexuality or aggression. Patients are typically unaware of or unconcerned about the social, occupational and financial consequences of their behavioral alterations. Cognitive deficits occur in the domains of attention, abstraction, planning and problem solving, reflecting an executive problem, whereas memory, language and spatial functions are well preserved. Speech output may become aspontaneous and limited to short phrases or stereotyped utterances. Echolalia is often observed. There often is a decline in personal hygiene and grooming. Overeating, altered food preferences and oral exploration of inanimate objects are frequently seen in patients with FTD.

It is increasingly recognized that varying degrees of frontal lobe dysfunction are present in motor neuron disease/amyotrophic lateral sclerosis (40), and 15% of cases of FTD have signs of motor neuron disease (41).

Pathology

At autopsy markedly gross atrophy of the frontal and temporal lobes is seen in FTD. On histologic examination the salient features include neuronal loss, micro-vacuolization and astrocytic gliosis centered on cortical layer II. The microtubule-associated protein tau has been found to be mutated in a family with FTD with parkinsonism (42). Immunohistochemical and biochemical techniques are now used to distinguish tau-related forms of FTD from non-tau forms, which mainly contain ubiquitin-positive intraneuronal inclusions (43).

Unfortunately, there is only moderate correlation between clinical and pathological findings: the same clinical syndrome can arise from two different pathologies and a single pathology can present as different clinical syndromes.

Imaging

MRI of patients with FTD often shows atrophy in the frontal and temporal lobes, which may be asymmetric (44). Functional imaging (PET or SPECT scans) have shown abnormalities in the ventromedial frontal cortex (often asymmetric) occur earliest (45). A longitudinal PET scan study showed that in the earliest stages FTD atrophy is limited to the frontal lobes and in later stages spreads into temporal and parietal cortices.

Epidemiology

Prevalence studies of FTD are inconsistent, giving ranges of 3.6 – 15.0 per 100,000 (46). There is a high familial occurrence of FTD (47). Some affected families from Great Britain, Australia and the U.S. have been traced to a common founder in North Wales (48). Genetic factors, specifically different alleles of apolipoprotein E, have been inconsistently linked to sporadic FTD (49, 50). The distribution of FTD is equal between men and women. Age at onset is typically between 45 and 65, and does not differ between familial and sporadic cases (51). The mean duration of illness from onset to death is 4 – 6 years, with a range of 2 – 20 years. Patients with tau-positive frontotemporal lobar degeneration survive significantly longer on average than those who are tau-negative (52). Progression to death in FTD is much more rapid than in AD (average of 4.2 years and 6.0 years, respectively), a pattern repeated in the rate of cognitive decline on Mini-Mental State Examination (MMSE) (53). FTD with motor neuron disease has been shown to be a much more aggressive disease process than FTD without motor neuron disease (54).

Biomarkers

Total tau in CSF is increased in AD and other dementias, and is considered a general marker of neurodegeneration. There are conflicting results on the diagnostic accuracy of CSF total tau and $A\beta_{42}$ for the diagnosis of frontotemporal dementia (55, 56). Recently developed immunoassays for the detection of CSF tau that is phosphorylated at specific epitopes (e.g., threonin 231) can distinguish well between Alzheimer's disease and FTD (57).

Treatment

There have been no large-scale double-blind, placebo-controlled clinical trials for the treatment of FTD, although several smaller trials (30 subjects at most) have been carried out. In these studies the use of the anticholinergic medication rivastigmine and other antidepressants have consistently been shown to improve behavioral symptoms but not cognition (58, 59).

Delirium: A Cautionary Note

Delirium and rapidly progressive dementia are easily confused with each other since they share many clinical features. Core clinical features of delirium include acute and fluctuating course, reduced level of consciousness, inattention and disorganized thinking. Delirium is thought to be caused by non-specific alterations in neurotransmitter and endocrine pathways, which subsequently alter cerebral metabolism. Changes in cognition, such as memory deficits, language disturbances or disorientation, are commonly seen in delirium. Some cases of delirium may evolve in a subacute time course and are often misdiagnosed as dementia. Delirium may be multifactorial and can be caused by almost any disease that affects the brain. Its causes may include toxic-metabolic disturbances and traumatic, vascular, infectious, neoplastic, epileptic, nutritional or psychiatric pathophysiologic entities. In-hospital delirium complicates up to 20% of all admissions (60), and its likelihood increases with each decade of age. Full recovery can be expected in most cases, although reversal of delirium can take weeks. Persistent deficits in memory or other cognitive skills may remain in some cases. Abrupt behavioral decline in patients with Alzheimer's disease or other dementias is more often caused by a secondary process than by an abrupt acceleration of the degenerative process. Almost any systemic or neurologic illness can cause a superimposed delirium in a patient with preexisting dementia. Very common causes are urinary tract infections with or without sepsis, pneumonia, unwitnessed trauma with related pain or medication errors. Less common are stroke, seizures, meningitis or subdural hematoma.

Conclusion

The past two decades have witnessed a fundamental shift in our appreciation of the aging mind, away from the inevitability of "senilility" and towards an appreciation of distinct diseases of late life that can impinge upon cognition. This shift in intellectual mindset has led to the identification of clear-cut dementia syndromes, etiologies and, most important, the first generation of treatments. The benign neglect of the dementia patient that characterized care for most of the past century has been pushed aside by the contemporary focus on diagnosis and treatment. Our purpose here is to review the current state of knowledge of the dementias most commonly encountered in clinical practice and provide an update on where current research is heading. In an aging population, clinicians will encounter increasing numbers of patients with dementia. In the 21st century these patients can now be approached with the hallmarks of clinical care identifying symptoms and syndromes, elucidating the underlying pathobiology and treating the etiologies.

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Schizophrenia from a Neuropsychiatric Perspective

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Abstract

Our understanding of schizophrenia has increased substantially in recent years. This is due to technological advances that have improved our ability to assess neuropsychiatric function and the genetic underpinnings of the disease. While diagnostic classification still relies on the presentation of the more overt symptoms of the disease, the neuropsychiatric perspective provides a more accurate and comprehensive understanding of the illness. This perspective provides insight into the etiology and treatment of schizophrenia. This article provides an overview of schizophrenia from the broad viewpoint of neuropsychiatry.

Key Words: Schizophrenia, neuropsychiatry, cognition.

SCHIZOPHRENIA IS A DISEASE defined by a number of symptoms that differ across individuals in their presence, frequency, severity, and topography. This heterogeneity in symptoms has complicated the search for the etiology of the disease and the mechanisms for its treatment. This article paper will review schizophrenia as a neuropsychiatric disease. Signs and symptoms of schizophrenia will be considered within the conceptual framework of neuropsychiatry, including aspects of consciousness and awareness, orientation, perception, cognitive impairments, affect, thought and language, and neurological soft signs. The classical symptoms of schizophrenia (e.g., positive symptoms such as delusions and hallucinations and negative symptoms such as blunted affect and social withdrawals) will not be reviewed specifically here, but will be discussed within the context of the neuropsychiatric domains, where appropriate.

Consciousness and Awareness

The study of consciousness and awareness has been complicated in general by the difficulty in utilizing these constructs. Consciousness has been defined in degrees to encompass a number of processes from the most basic (e.g., a simple response to sensory stimulation) to the awareness of one's own complex thought processes. These constructs rely heavily on a phenomenological approach, and difficulties in the assessment of internal experiences are well understood. It is difficult to assess and quantify these constructs because patients with schizophrenia rarely accurately describe such overt behaviors as symptoms (1) and their own functional abilities (2). Therefore, assessments of internal experiences that rely on self-reporting are likely to have questionable validity.

The process of self-monitoring allows individuals to distinguish self-generated thoughts and behaviors from those generated by others. This cognitive process has been used to attempt to explain some schizophrenic symptomatology. For example, patients with schizophrenia, particularly those with positive symptoms such as hallucinations and delusions, tend to have deficits in self-monitoring (3). These monitoring deficits may have a causal relationship with clinical symptoms, since schizophrenia patients with hallucinations or formal thought disorder (compared to schizophrenia patients without these symptoms and healthy individuals) have deficits in the ability to match their own behavior with its consequences (4). Delusions, especially those that heavily influence behavior, are also associated with deficits in monitoring the origin of one's ideas and the reasons for one's actions (5). Patients with auditory hallucinations tend to misperceive internal stimuli as originating from the external environment, and these misperceptions can be tactile (6), verbal (7, 8), or visual in nature (9). Taken together, these findings suggest that deficits in self-monitoring may underlie some symptoms of schizophrenia, particularly delusions

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and hallucinations. This is particularly relevant because the cognitive causes of these experiences have proven difficult to identify in previous research.

Cognitive abilities such as attention, memory and problem solving are important predictors of everyday functional outcomes, such as independent living, interpersonal relationships, and occupational success. While cognitive impairments may be the single best predictor of everyday functioning outcomes, they are not particularly strong predictors. For example, a considerable amount of the variance in these everyday outcomes is not accounted for by impaired performance on cognitive tests. Some of this lack of overlap may be accounted for by social cognition, which has emerged recently as an important concept in understanding the impact of the disease. Abilities in this domain include the identification or recognition of another person's emotions (and by inference their internal experiences) based on his or her facial expression or tone of voice (10, 11). An important theoretical model of social cognition is the Theory of Mind, which posits that people make sense of the world by conceptualizing their own and others' behaviors in terms of their own beliefs and desires (12). Deficits in social cognition secondary to the Theory of Mind have been used as a partial explanation for the social withdrawal into autism that has been described in schizophrenia since the 19th century (14). Schizophrenia patients with negative symptoms may show some signs of exaggerated social withdrawal, and many of these patients have difficulty explaining their own or making sense of others' internal experiences; these deficits in social cognition are not a consequence of cognitive impairment (13).

Assessment of "metacognitive" processes is another mechanism associated with consciousness and awareness. As distinguished from self-monitoring, described above, which is the ability to identify the origin of stimuli, metacognitive processes involve the ability to monitor the nature and quality of one's cognitive operations and to regulate behavior and thought in response to changing external stimuli. The consideration of these monitoring processes may also assist in making the results of cognitive testing more generalizable to the patient's behavior in the real world. For example, schizophrenia patients' performance on formal neuropsychological tests measuring cognitive abilities such as verbal memory, problem solving, working memory, and processing speed accounts for only a modest amount of variance in explaining everyday functioning (14, 15). Moreover, the relationship between cognition and real world functioning may be mediated by other symptoms of the illness (16) and external environmental barriers, such as social conditions and decreased incentive to seek employment due to disability payments (17).

Since it is more "ecologically" valid (i.e., generalizable to the real world), deficits in social cognition should explain some part of the functional deficits in schizophrenia. While it is not yet largely represented in the literature base, there is some evidence that impairments in social cognition are not fully determined by the severity of other cognitive deficits (18) and that social cognitive factors may mediate the relationship between neurocognition and functioning in the real world (19). This influence might occur because the ability to realistically evaluate one's competence, likelihood of success in performing skilled acts, and reactions of others to one's behavior is an integral part of real-world functioning. If one is highly competent but unaware of this competence, the likelihood of attempting skilled acts would be reduced. If one overestimates one's ability or misperceives others reactions to them, then one's behavior may be poorly matched in the environmental situation, increasing the likelihood of failure, regardless of level of skill.

Koren and colleagues (20) have proposed experimental paradigms for assessing metacognitive skills that measure confidence and control over responses to traditional cognitive tasks. For example, many typical problem-solving tasks require a careful step-by step process in which each successive step is informed by the results of the immediately previous strategic effort. If, however, the ability to estimate the reasons for failure is reduced or, particularly, if the ability to detect failure is reduced, then the likelihood of developing a successful trial and error strategy is grossly limited. Thus, people with schizophrenia may fail in problem-solving tests not because of a global deficit, but rather because of highly specific deficits in applying information that they have just learned (e.g., the accuracy of their last response) to their next problem-solving step (i.e., their next response). These paradigms offer a methodology that provides some additional information that goes beyond correctness of responses on test items in terms of understanding the complex task of interacting with the external environment.

Orientation

Cognitive deficits and poor self-awareness are cardinal features of schizophrenia; gross disorientation to time and place is not as commonly found.

An exception is found in patients with a very adverse course of illness and severe progressive cognitive impairments; in such cases, disorientation to time and place may be present (21). Most schizophrenia patients do not appear to be disoriented to person, and they are typically oriented to time and place. However, a substantial minority (approximately 25%) of younger patients tend to be disoriented with regard to their age (22, 23). In later life, schizophrenia is associated with a worsening of cognitive performance that often resembles dementia in its severity and scope, with multiple, generalized, severe-to-profound cognitive deficits (24, 25). Age-disorientation is a stable and more common feature of the illness in later life and is most common in patients with severe global cognitive impairment (26). Its stability, along with a lack of correlation with treatment history, premorbid adjustment, education, or amount of social interactions (27, 28), suggests that this feature may be a trait of some patients and predictive of poorer everyday outcomes and poor response to antipsychotic treatments as well.

Perceptual Organization

The ability to organize sensory input is a fundamental basis for cognition. Obviously, any dysfunction in sensory systems will have consequences for higher-order cognitive processes. While perceptual dysfunction is found in a number of patients across sensory modalities, there is evidence that these deficits are specific to a limited subset of patients with the illness. As mentioned above, schizophrenia is a disorder characterized by heterogeneity across individuals with the same diagnosis and within-patient variability in symptom severity over time. We noted earlier that certain deficits in self-monitoring appear to be associated with positive symptoms. On the other end of the schizophrenia spectrum are patients who might not have frank psychosis through much of their illness, but have many negative symptoms. These patients, with negative and disorganized symptoms as opposed to predominantly positive symptoms, display poorer perceptual organization (29, 30). Similar findings of poorer perceptual organization have been found in those with deficit syndrome (31), those with poorer premorbid social functioning (32), and in patients in the chronic phase of the illness (33).

A series of studies by Javitt and colleagues have identified early (i.e., basic) visual and auditory processing abnormalities in schizophrenia. These impairments probably contribute to the more obvious and frequently studied higher-order cognitive processes and may provide some explanatory potential for deficits in object recognition (34) and auditory recognition (35), and underlie impairments in social cognition (36). It will be interesting to determine whether these cognitive impairments are as closely associated with functional outcomes, or not. If these deficits, which might be easier to target with specific pharmacological agents or behavioral strategies, correspond to improvements in higher-order cognitive processes, one might be more likely to see real world treatment effects.

Cognitive Impairments

Cognitive deficits were described as primary features of schizophrenia in the seminal descriptions of the disease (37, 38). Much of the research and treatment focus since these early descriptions, however, has been on the more obvious features such as positive symptoms and thought disorder. A return to the study and, later, treatment of cognitive deficits in schizophrenia has followed two trends. Evidence of lack of treatment progress throughout the 20th century (39) raised concerns that treatment of positive symptoms of the illness, though necessary, was not sufficient for recovery or even promoting independent living in many cases. Additionally, a growing body of work suggested that cognitive deficits were the best predictors of dysfunction across many domains, such as interpersonal relations, occupational skill acquisition and work success, and treatment success (14, 15). In this article, we provide a brief review of cognitive impairments in schizophrenia. See Bowie and Harvey (40) for a comprehensive review of this important topic area.

Cognitive impairments are found across most domains (e.g., attention, working memory, verbal fluency, processing speed, executive functions, verbal memory) in the vast majority of schizophrenia patients. These impairments tend to be moderate in magnitude (i.e., one to two standard deviations below the performance mean of healthy individuals), with superimposed severe deficits in domains such as verbal learning and executive functioning (41). Even patients who perform within the normal range of functioning on neuropsychological tests are impaired relative to their estimated intellectual functioning (42). Thus, it has been proposed that cognitive impairment is universal in schizophrenia (43). Deficits in cognition are considered a primary feature of schizophrenia because they are detectable even before the onset of frank psychosis (44). Cognitive deficits are also detectable in healthy first-degree relatives of schizophrenia patients (45), and in individuals on the schizophrenia spectrum who do not meet criteria for schizophrenia (46) and are independent of other symptoms (47). By the time of the first episode of psychosis, deficits are present and moderate-to-severe across many domains (48) and mild intellectual decline appears to occur during this first episode (49). Cognitive dysfunction appears to remain stable in its severity and topography through middle age (50). However, in late life, global declines may occur in chronically ill patients (24, 25), but declines in patients with a less chronic course have been reported to be much more specific, possibly restricted to complex information-processing tasks that measure processes that are difficult to observe clinically and detectable only with specific neuropsychological instruments (51, 52).

Affect

Disturbances in affective expression (e.g., blunted affect) and experience are hallmark negative symptoms in schizophrenia. It is generally accepted that negative symptoms represent a distinct feature of the illness (53). The expression of affect is distinct from other negative symptoms such as social dysfunction and disorganization (54), and shares less variance with cognition, outcome domains and positive symptoms. Blunted affect has been incorporated into a categorical model of schizophrenia known as the deficit syndrome (55). These patients, with severe emotional blunting and little interest in purposeful activities, are characterized by a particularly poor course of treatment for refractory schizophrenia.

Depressive symptoms, also present in many schizophrenia patients (56), are difficult to distinguish from blunted affect. Recent work suggests that self-reported depressive symptoms are an important barrier to occupational and interpersonal performance, independent of cognitive dysfunction and other symptoms. They may serve as rate-limiting factors in patients with schizophrenia, in that they may be a hindrance to real world *performance* even in patients who have the *ability* to perform tasks (16). The presence of mood symptoms, such as depression and mania, contributes to the diagnostic distinction between schizophrenia and schizoaffective disorder. Mood symptoms are a necessary consideration for clinicians, because they can further interfere with the patients' functioning (16) and quality of life (57).

Thought and Language

Along with negative and positive symptoms, organized thought disorder has constituted a fundamental feature of schizophrenia throughout its diagnostic history. Thought disorder, measured by language output, has three common manifestations. It can be characterized by a paucity of speech with limited expression of thoughts; by poor connectedness, referred to as loosening of associations; or by unusual and/or illogical thinking.

Schizophrenia patients often (up to 40% of consecutive samples) display poverty of speech, defined as a reduction in the amount of speech. These patients typically offer little information voluntarily, and their responses to questions are often perfunctory and brief. Alternately, approximately 25% of patients with schizophrenia may have pressured speech, similar to those with mania, where it is more commonly observed. This may manifest as an increase in the amount of words offered (which is often accompanied by abnormalities in the connectedness of speech, described below), the rate of speech, or increased volume and pitch.

Disconnected speech is distinct from poverty of speech in schizophrenia, in that it typically involves an excess of speech. Examples of disconnected speech include circumstantiality (long-winded and wandering speech that circles the topic area without really describing it), derailment (speech that shifts away from the topic area), tangentiality (off-topic responses to questions), and loss of goal (speech that is completely removed from the topic). This manifestation of thought disorder occurs at a higher rate in schizophrenia, with approximately 56% of patients displaying derailment.

Other evidence of communications abnormalities includes unusual symptoms such as neologisms (personally created words that hold a unique meaning to the speaker), word approximations (real words that are assigned a new meaning), clanging (speech that is connected by rhymes or other phonological mechanisms), and echolalia (repetition of another speaker's words). These aspects are less common (e.g., 2% display neologisms) than disconnected speech and poverty of speech. Thus, although they are highly distinctive, they are not useful diagnostic indicators.

The causes of thought disorder in schizophrenia are still being explored. Some models suggest that they are attributable to failures to monitor the source of information (58), i.e., the patient manifests difficulty in discriminating the source of information in short-term memory, confusing internal thoughts with externally presented speech. Schizophrenia patients demonstrate errors in context processing, or the ability to use information from the surrounding environment to facilitate the efficient processing of information (59). Barch and

Berenbaum (60) found that different aspects of formal thought disorder could be reliably observed by manipulating the context in which the speech was produced. Another potential causal mechanism of formal thought disorder is related to deficiencies in the structure of semantic networks. Patients with schizophrenia have difficulty accessing semantic information (61), and their language output tends to be poorly organized in terms of semantic relationships (62). Disconnected speech is relatively stable over short-term follow-up periods, with a general increase in underproductivity in later life (63).

Conclusions

Schizophrenia is a complex disease that manifests with a heterogeneous profile across patients. Conceptualizing the illness from the perspective of neuropsychiatry enables the practitioner to better understand the most clinically relevant aspects of the disease. It is now well understood that cognitive impairments are present and substantial in nearly all schizophrenia patients, even those experiencing their first episode of psychosis. These deficits may become more marked in later life and are an important treatment target, because they are the best predictor of a patient's level of interpersonal skills, occupational functioning, and self-care. Although patients' cognitive impairments are severe and they may be disoriented as to their own age, they do not typically evidence disorientation to person, time or place. An important clinical distinction involves negative versus affective symptoms. Depressive symptoms have at least a semantic overlap with the negative symptoms of schizophrenia, yet they appear to be distinct features of the illness. There are therapeutic implications for distinguishing affective from negative symptoms, making careful examination of these symptoms necessary in clinical practice.

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Neurobehavioral Consequences of Traumatic Brain Injury

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Abstract

At least 1.4 million people die, or receive hospital or emergency care every year in the United States as a result of traumatic brain injury (TBI). Many more are treated in other settings or receive no treatment at all. Thus TBI is often unidentified, with subsequent cognitive, behavioral, emotional and physical sequelae that are not linked to the injury. Yet, over 5.3 million Americans live with TBI-related disabilities that interfere with their overall performance and social roles within the community. The pathophysiology and consequences of TBI are discussed, as are functional changes and psychiatric manifestations after TBI. Finally, implications and recommendations for clinical practice are reviewed, including the importance of screening for TBI.

Key Words: Traumatic brain injury, neuropsychiatry, rehabilitation, axis I disorders, psychiatric disorders.

Introduction

TRAUMATIC BRAIN INJURY is the leading cause of death and lifelong disability in the United States for individuals below the age of 45. Current estimates from the Center for Disease Control (CDC) indicate that at least 1.4 million Americans sustain a TBI annually (1). Of these individuals approximately 235,000 are hospitalized, 50,000 die, and 1.1 million are treated and released from emergency departments. Approximately 90,000 are left with permanent disabilities each year (1). As a result, more than 5.3 million people, approximately 2% of the U.S. population, and about 57 million world-wide, are living with disabilities secondary to their brain injury (1, 2). While these numbers are large, the CDC acknowledges that these figures are actually an underestimate of the actual number of people living with TBI, because the data only include individuals who die or obtain medical services in hospitals and emergency departments. Typically, these are individuals who have sustained a documented loss of consciousness (LOC) or a period of confusion or altered mental status, and in some instances, have positive neuroimaging findings (i.e., computed tomography [CT], magnetic resonance imaging [MRI]) (1). A majority of individuals do not exhibit neuropathology on neuroimaging after TBI (3) and, often, the report of the duration of LOC or post-injury confusion is uncertain, particularly if there were no witnesses to the event precipitating the TBI. CDC incidence figures do not include people treated in federal, military, or VA hospitals, or the estimated 528,000 individuals with TBI who were treated in physicians' offices (439,000) or in outpatient settings (89,000) (4). People who do not seek medical attention are also not included; this represents a number estimated to be equal to 25% of the number of individuals with mild or moderate TBI (5). Given that a majority of TBIs are mild, this number is likely to be several hundred thousand each year. In many instances, no link is made between the blow to the head the person sustained and subsequent physical, cognitive, behavioral or emotional sequelae. TBI has been called the "silent" or "hidden" epidemic because many individuals are

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not identified by the health care system and their neurological, neuropsychological and neurobehavioral symptoms and functional difficulties are attributed to etiologies other than brain injury (6–11).

The consequences of TBI are often devastating to the individual and their loved ones. Significant physical impairments often occur, including headaches, sleep problems, fatigue, blurred vision, dizziness, loss of hearing, and in a small percentage of cases, seizure disorders (12, 13). Even more prevalent are changes in cognitive, behavioral and emotional functioning. Cognitive complaints are typically reported in the areas of memory, attention, and executive functioning (14). Additionally, increased irritability, depression or anxiety is often reported by individuals who suffered from a traumatic brain injury, or identified by those close to the person (15). Behavioral changes may include the presence of impulsive behavior, reduced frustration tolerance, lack of empathy, emotional lability, apathy or aggression. This variety of symptoms is often not associated with the TBI by the individual, his or her family, or primary health care providers, particularly when the subject has experienced a "mild" TBI or "concussion" (16, 17). This lack of identification can lead to no treatment or to inappropriate treatment (18–20).

Consequences of Injury

TBI severity is defined by the duration of LOC, altered mental status (e.g., confusion) or post-traumatic amnesia (PTA) (21). It is important to note, however, that the severity of functional impairments after TBI often is not related to the severity of the injury (21, 22). Patients are classified as having a moderate-to-severe TBI if they have a LOC over 30 minutes or altered mental status greater than 24 hours or Glasgow Coma Score below 12 (16, 21). Although many individuals who experience a moderate-to-severe injury have some functional impairments after the injury, they usually receive inpatient, and possibly outpatient, rehabilitation services to address these impairments. However, this is rarely the case with individuals who sustain a mild TBI. Mild TBI is defined as a blow to the head followed by a LOC of less than 30 minutes, an altered mental status with PTA of less than 24 hours or Glasgow Coma Scale score of 13–15 (16). In fact, many professionals mistakenly assume that individuals who experience a mild TBI will make a full recovery of functioning within a brief period of time (16, 17). For a majority of those with a mild TBI, this assumption is warranted and full recovery occurs within 3–6 months (23, 24); however, a significant minority, approximately 15%, will continue to experience long-term cognitive, physical and behavioral difficulties that interfere with their ability to function (25–30). This condition is also known as Persistent Post-Concussion Syndrome (PCS) (12, 25, 31). Despite its counterintuitive name, "mild" TBI can result in significant post-injury impairment (22). Because these consequences are not well understood, family members and many professionals may assume that these individuals are exaggerating their symptoms or "faking" (32, 33). As a result, emotional or behavioral problems are seen as psychogenic (34, 35). However, as noted above, the symptoms are most likely secondary to neurological event and not primarily psychiatric (36).

Etiology of TBI

TBI results from an external force applied to the skull (including inertial force), leading to temporary or permanent pathology. While direct, focal injuries can occur as the brain makes contact with the sharp bony surfaces of the skull, a majority of TBIs result in widespread shearing and stretching of nerve fibers (diffuse axonal injury) caused by the rapid acceleration and deceleration of the brain. The diffuse nature of the injury contributes to a broad range of symptoms, including impairments in arousal, attention, mood, and behavior. The frontal and temporal lobes are common sites of damage that may lead to disruption of the closely linked limbic system thought to be involved in the modulation of emotional, motivational, and behavioral processing (33, 37).

Until recently, most TBIs were the result of motor vehicle accidents (MVAs), but the CDC's most recent report (1) reveals that falls are currently the leading cause of TBI, with rates highest for children under 4 and adults over 75 years of age. MVAs are second, with physical assaults and sports-related injuries accounting for a majority of the remaining TBIs reported each year.

Functional Changes

The severity of the injury is not necessarily associated with the extent of the person's functional impairments (3, 22) and post-TBI functioning is multifactorial. Physical changes reported by individuals after brain injury may vary and can be independent of the severity of the TBI. Symptoms may include: fatigue, clumsiness, decreased sensory functioning (i.e., changes in hearing, vision, smell and taste), dizziness, changes in appetite, seizures, and difficulties with sleep and temperature regulation (38, 39). Sensory loss has been reported as long as ten years after TBI (40), with impairments of smell (41) and hearing (40) being most commonly reported. Fatigue, described as exhaustion after simple and routine physical or mental tasks (42–44), is one of the most common physical symptoms reported after TBI. This problem is often complicated by disruptions in the sleep cycle. Lack of sleep and daytime sleepiness can further impair cognition, behavior and mood, and can undermine treatment. Additionally, chronic pain (45) and headaches, in particular, commonly follow even mild brain injury (44–46) and can interfere with cognitive functioning.

Cognitive problems following TBI include impaired attention and concentration, reduced processing speed, word finding difficulties, altered academic abilities (i.e., errors in simple math computation, spelling difficulties, and difficulties understanding what one reads) decreased memory and learning abilities, and impaired executive functioning (i.e., reduced ability to plan, sequence, prioritize, think flexibly, abstract or problem solve) (14, 38). Since a high percentage of individuals with TBI sustain damage to the frontal lobes or to the frontal system, impairments of higher level thinking or executive functioning are common (33, 37). In addition to executive dysfunction, memory problems are almost always present following TBI, either due to direct effects on memory systems or secondary to disrupted attention and concentration (33, 47–51). Often, the severity of cognitive deficits does not become apparent until the individual tries to resume the activities of preinjury life, such as return to work (52).

Besides physical and cognitive symptoms, many individuals with TBI experience various types of behavioral dyscontrol (e.g., impulsivity, aggression, amotivation, apathy) and emotional dysregulation (e.g., moodiness, irritability, apathy) (53), which can disrupt the individual's social interactions and employability (38, 54–56). Impaired interpersonal communication and social cognition (e.g., an inability to follow conversations, being rude, interrupting people, talking too fast or too slowly) also impact the person's ability to develop and maintain meaningful relationships (57).

Co-occurring Psychiatric Diagnoses

In addition to physical, cognitive and behavioral changes that occur following TBI, a majority of individuals with TBI are diagnosed with one or more newly acquired psychiatric diagnoses after injury (15, 58). Alterations in mood can arise as the individual with TBI recognizes that the impairments associated with the injury have not resolved. Individuals often describe changes in the self and loss of defining personal attributes. These changes can lead to feelings of depression or anxiety (59). This realization is often compounded by description of the individual by friends and family as a "different person." Although emotional distress, most commonly in the form of depression and anxiety, is the most prevalent psychiatric disorder for many individuals immediately after injury, some resolution in psychological symptoms typically occurs over time. However, longitudinal studies have suggested that a substantial proportion of individuals with TBI either continue to experience or develop late-onset psychiatric disorders (60) for as long as 30 years after injury (61).

Major depression is the most prevalent psychiatric disorder after injury, with estimated rates ranging from 14–77% (13, 15, 58, 61–66), with approximately 60% meeting a diagnosis of depression at some point after injury (67) and about 20% at any given time after TBI (58). Other frequent psychiatric disorders after injury include substance abuse, ranging from 5–28% (58, 64, 66), posttraumatic stress disorder (PTSD), with prevalence rates ranging from 3–27% (15, 58, 64, 65, 68), other anxiety disorders, which affect from 3–28% of persons with TBI (15, 58, 62, 64–66, 69) and personality disorders (70). Sampling (community vs. clinical settings) and measurement variability may account for the different prevalence rates reported across studies (71). However, regardless of the methods used to sample, these rates remain consistently higher than in the general population (13, 15, 58, 61, 62, 64–66). While the risk for developing psychiatric symptoms is highest in the first year following injury (58, 66), the risk for developing these disorders remains elevated for decades after TBI (61, 65, 72). Furthermore, these disorders are often comorbid. Depression and anxiety are especially likely to co-occur with substance abuse (13, 58, 64, 66, 73).

The development of psychiatric disorders following TBI, particularly the comorbidity of psychiatric disorders and substance abuse, can increase the risk of other neurobehavioral problems, often creating obstacles for reintegration into the community (71, 74). For example, individuals who have experienced a loss of consciousness are four times more likely to attempt suicide than those who have not (69). Additionally, Simpson and Tate (73) reported that co-morbid depression and substance abuse in individuals with TBI increased the risk of suicide twenty-one times. Thus the co-morbidity of axis I disorder significantly increases suicidality. While numerous neurobiological (i.e., injury-related) and psychosocial factors contribute to the development and persistence of psychiatric disorders after TBI (75), factors such as length of time since injury, severity of injury, duration of LOC, age, gender, years of education, and ethnicity have not been found to be predictive of who develops psychiatric disorders after TBI (13, 15, 58, 62, 63, 65). However, pre-morbid psychiatric history, in particular, pre-existing personality disorders, has been associated with having a greater risk for developing additional psychiatric disorders after injury (15, 58, 61).

Implications for Clinical Practice

Consistent screening for TBI is important, especially in practices involving populations where "hidden TBI" is known or suspected to be common. This includes psychiatric populations (including substance abuse), individuals routinely exposed to violence (domestic violence), athletes and the elderly. Detailed histories should be taken to identify instances of blows to the head resulting in LOC, PTA, or altered mental status. These may be numerous and may have occurred weeks, months, or years prior to the current encounter with the health care system. When such events are identified, it is important to determine whether they predate the onset of presenting, potentially TBI-related symptoms.

Negotiating the health care system presents individuals with TBI and health care practitioners with a variety of challenges. Cognitive deficits may make it difficult for individuals with TBI to participate actively in maintaining their health and managing their own health care. Monitoring their health status and health problems and communicating with the representatives of the health care system can become burdens that the person with TBI is unable to cope with without some degree of assistance. Even when primary care providers and specialists spend significant time with these individuals, the cognitive deficits can still create barriers to effective treatment. The impact of these limitations is that the health care of the individual with TBI is often compromised.

Attention impairments can make it difficult to remain focused in interactions with health care staff. Filling out long checklists or forms can also be difficult with attention and concentration problems. Doing two activities simultaneously like providing one's medical history while being examined may be particularly challenging. Memory impairments in the individual with TBI can impact health care treatment because of difficulty in remembering details of one's medical and medication history, remembering topics to discuss with the health care provider or specific documentation to bring to appointments, and difficulty following through with prescribed interventions and medications. Reductions in processing speed can make it difficult to take in and respond to new information. Individuals with TBI may need to have additional time to complete forms and checklists, process health care information, and plan health care options. Executive dysfunction can affect the ability to plan health care, organize treatment appointments and follow-up care, prioritize information, remain focused and "on topic," regulate emotional responses (e.g., withdrawal, anger) if the individual becomes frustrated during interactions with the health care system. The person may feel easily overwhelmed and accompanying fatigue, embarrassment or humiliation can lead to avoidance of health care providers and failure to follow through with treatment. Health care practitioners need to recognize, anticipate, and accommodate these difficulties when dealing with patients with TBI.

Cognitive remediation is a recommended evidence-based intervention (76–78) for addressing the numerous cognitive sequelae of TBI. It is effective in managing specific domains of cognitive deficit such as attention and memory problems as well as improving functional and vocational outcomes and community integration (76–78). Remediation can thus help persons with TBI in negotiating the health care system more effectively. When possible, individuals with TBI should have a neuropsychological evaluation to determine the nature and extent of the cognitive impairments and plan treatment. Remediation, which may be coupled with psychotherapy, can then be provided by rehabilitation psychologists or neuropsychologists, in conjunction with speech therapists, occupational therapists, and other rehabilitation professionals.

Conventional wisdom and clinical reports indicate that psychopharmacology can be effective in treating neurobehavioral symptoms after TBI (79), including behavioral dyscontrol (e.g., aggression, irritability) and emotional turmoil (e.g., depression, anxiety). There is some evidence that depression after TBI is amenable to pharmacologic intervention, alleviating not only the mood disturbance but also reducing other physical (e.g., fatigue, headache) and cognitive symptoms (e.g., inattention, poor concentration) (80). However, it is essential to start medications with low doses, possibly sub-therapeutic, and titrate the medication slowly with continuous reassessment of symptoms because of high susceptibility to adverse effects for individuals with TBI (79). Medications that are highly sedative or have deleterious effects on the central nervous system also should be avoided for similar reasons (79, 81), including further memory impairment. Frequent reassessment is also necessary to assure that the individual remembers to take the medication, monitor side effects and treatment efficacy, especially since there are very few well-controlled studies examining the efficacy of various commonly used medications (78).

Consultation with a neuropsychiatrist familiar with the evaluation and treatment of psychiatric disorders following TBI may be of benefit to persons with TBI, their families, and clinicians providing care. Additionally, cognitive remediation and psychotherapy also can be instrumental in addressing changes in identity after TBI and improving emotional disturbances (e.g., depression, anxiety) (78, 82).

Conclusion

The high prevalence of TBI suggests the need for clinicians to consistently screen for TBI, particularly due to the large number of unidentified cases. Having knowledge of an individual is important, especially in practices involving populations where "hidden TBI" is known or suspected to be common. General practitioners should be aware of the possible long-term sequelae of TBI in order to provide appropriate education to individuals with TBI (83–85). In addition, the large number of possible co-morbid conditions following TBI may require a multidisciplinary approach to address symptoms such as headaches, sleep disorders, sensory disturbances (e.g., blurred vision, loss of hearing, imbalance), or seizures. It is critical to understand the link between common features of TBI and the common neuropsychiatric sequelae of brain injury, to adequately evaluate the individual with TBI (83, 86). Appropriate educational and neuropsychological intervention is critical to ensure positive outcomes, especially over the first year or two after injury. Explaining the possible neurocognitive and neurobehavioral sequelae and recovery pattern for TBI to the individual and involved caregivers can maximize recovery and effective treatment plans (85). The primary care physician can play a major role in monitoring progress and intervention, and in maximizing an improved outcome.

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Neuropsychiatric Disorders Following Vascular Brain Injury

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Abstract

Several neuropsychiatric disorders such as mood, anxiety and psychotic disorders occur following cerebrovascular lesions. Post-stroke depression is the most common of these disorders and, along with post-stroke anxiety, has been shown to inhibit physical and cognitive recovery. Antidepressants have been shown to effectively treat post-stroke depression and to have a positive impact on rehabilitation efforts in patients suffering from this disorder. Much less is known about the potential impact of psychiatric conditions on recovery after stroke. Controlled trials will be able to adequately determine the effectiveness of treatment for these disorders.

Key Words: Stroke, neuropsychiatric disorders, review.

Introduction

Despite a steady decline in the incidence of strokes over the last 50 years, due to improvement in the treatment of diseases such as hypertension, diabetes mellitus and hypercholesterolemia, this disorder continues to represent a major health problem. Stroke is the second leading cause of death worldwide. According to estimates of the American Stroke Association, about 750,000 strokes occur annually in the U.S. and, as a result of improvement in the acute management of this disorder, there are about 4.5 million stroke survivors in the U.S. (1). Neuropsychiatric disorders related to stroke are prevalent (Table 1; 2–15). This article will address a number of these disorders and their impact on recovery from stroke.

Post-stroke Depression

Depression is the most frequently occurring psychiatric disorder after stroke. It has been consistently associated with poor cognitive status (16) and functional outcome (17, 18) in stroke survivors. Despite its prevalence, it has been reported that general practitioners underdiagnose post-stroke depression (PSD) in up to 80% of cases (19). This is thought to be due to lack of awareness of this disorder.

Diagnosis

Despite adopting a non-etiological view to define most psychiatric syndromes, the Diagnostic and Statistic Manual of Mental Disorders, Text Revision, 4th edition (DSM-IV-TR) (Table 2) contemplates for PSD a diagnosis of "mood disorder due to stroke with depressive features." However, since this concept lacks the syndromic specificity of affective disorders, PSD has been mostly defined, for research purposes, as either major or minor depression according to the Research Diagnostic Criteria (20).

The DSM-IV-TR symptom criteria for PSD involve signs or symptoms frequently observed in stroke patients who are not depressed, such as hypomimia, motor or speech retardation, apathy, insomnia or decrease in appetite (21). Thus, there is a lack of consensus among different research groups on the most appropriate method for diagnosing PSD when cognitive or neurovegetative symptoms result from physical illness (22, 23). While some researchers advocate the use of an inclusive approach in which depressive diagnostic symptoms are counted regardless of whether they may be related to physical illness (24), others favor an etiologic approach. Using the etiologic approach, a symptom is counted only if the diagnostician feels that it is not the result of physical ill-

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TABLE 1
Prevalence of Post-Stroke Neuropsychiatric Disorders

Syndrome/Investigator	Setting	N	Prevalence
Depression			
Burvill et al. (2)	Community	294	23%
House et al. (3)	Community	89	23%
Eastwood et al. (4)	Rehabilitation unit	87	50%
Morris et al. (5)	Rehabilitation unit	99	35%
Astrom et al. (6)	Acute hospitalization	80	25%
Anxiety Disorder			
Leppavuori et al. (7)	3–4 months post-stroke	277	20.6%
Castillo et al. (8)	Acute hospitalization	309	27%
Mania			
Starkstein et al. (9)	Acute hospitalization	700	3 cases
Dunne et al. (10)	Acute hospitalization	661	3 cases
Anosognosia			
Stone et al. (11)	Acute hospitalization	69 right side stroke	28%
		102 left side stroke	5%
Pathological Affect			
Piamarta et al. (12)	Acute hospitalization	33	48.5%
Calvert et al. (13)	Acute hospitalization	448	21.5%
Apathy without Depression			
Starkstein et al. (14)	Acute hospitalization	80	11%
Brodaty et al. (15)	3–6 months post-stroke	167	26.7%

TABLE 2
DSM-IV-TR Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a Mixed Episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

ness (25). Thus, there is a need to determine what symptom clusters have diagnostic validity in PSD.

To examine the phenomenology of post-stroke depression, Gainotti et al. (26) developed a scale to compare patients with PSD to patients admitted to a psychiatric unit with a diagnosis of primary major depression (i.e. not due to a general medical cause). PSD patients exhibited higher scores in the following items of this scale: catastrophic reactions, hyperemotionalism, and diurnal mood variation. Moreover, among 142 stroke patients, Fedoroff et al. (27) found that at 2-year follow-up, depressed patients exhibited a significant higher frequency of all the assessed vegetative and psychologic symptoms, except for guilt and self-deprecation.

Prevalence

The prevalence of PSD has been examined by numerous systematic reviews (28, 29). Different factors, including the setting (in-hospital vs. community surveys) and time frame (acute post-stroke period vs. several months after the stroke) of epidemiological studies, contribute to the reported differences in the prevalence rates of PSD. Other factors that complicate the diagnostic accuracy are methodological limitations such as the lack of standardized criteria for diagnosing PSD (30–32) and the difficulty in assessing the presence of mood disorders in patients who might exhibit post-stroke residual cognitive and language impairments.

A systematic review by Robinson (33) reported that the mean frequency of major depression among stroke patients in acute and rehabilitation hospitals was 19.3% while the mean prevalence of major depression among stroke patients studied in community settings was 14.1%. Consistent with these findings, a review of prevalence studies by White and Mulsant (29) demonstrated a greater occurrence of PSD in hospitalized patients compared to patients in the community, reflecting a reciprocal relationship between depression and post-stroke-persistent physical disability. This review also found that the prevalence of major depression was higher when patients were studied soon after their stroke.

Clinical Course

Results from several longitudinal studies that examined the duration of PSD suggest that PSD can extend up to 3 years from the acute phase of the stroke (34). In a longitudinal study, Morris et al. (5) found that the mean duration of post-stroke major depression was 39 ± 31.8 weeks, whereas the mean duration of minor depression was only 12.2 ± 18.2 weeks. Another longitudinal study by Astrom et al. (6) followed 80 PSD patients for a 3-year period and found that 30% of patients with in-hospital major depression remained depressed at 1-year follow-up. Of them, 25% remained depressed at 2-year follow-up while at 3-year follow-up 20% were still depressed.

A longitudinal study of acute stroke patients by Burvill et al. (35) reported that at 24 months follow-up, patients who had in-hospital minor depression had a significantly higher frequency of depression (major or minor) compared to patients with in-hospital major depression. These results suggested that while major post-stroke depression has a natural course of less than 1 year, minor depression is often more persistent.

Premorbid Risk Factors

Little is known about the risk factors for developing depression after stroke. Knowledge of these factors would allow clinicians to initiate, during the acute post-stroke period, measures to better target prevention and treatment of PSD.

In a prospective study that examined the contributions of neurobiological, functional and psychosocial factors to PSD by Astrom et al. (36), a population-based cohort of 80 patients with acute stroke was assessed for a period of 3 years for the presence of depression, functional ability and social network. Left anterior brain lesion, dysphasia and living alone were found to be the most important predictors of immediate major depression after stroke. While at 3 months post-stroke the most important predictor for depression was dependence in activities of daily living, at 3 years post-stroke, generalized cerebral atrophy was the most important predictor. There is a need for further research to elucidate this correlation between cerebral atrophy and function. Specifically, there is a need to correlate focal versus generalized atrophy with the underlying pathology and outcome. A more recent study by Morrison et al. (37) that also assessed stroke patients repeatedly for a 3-year period, reported that earlier levels of functional deficit and anxiety are significant predictors of depression at follow-up. A study by Spalletta et al. (38) reported that predictors of cognitive function and depression severity are different in subjects with different laterality of lesion. These authors showed that PSD is associated with cognitive impairment only in patients with left-brain lesions.

A systematic review by Hackett and colleagues (28) found that most studies consistently associated physical disability, stroke severity and cognitive impairment with depression. However, this review also demonstrated that major limitations such as variable selection and poor statistical methodology present in these studies still prevent the identification of patients who are most at risk of developing PSD.

Anatomical Correlates

Many investigators have attempted to find a correlation between lesion location and PSD in order to delineate an organic hypothesis for the emergence of depression in a subpopulation of stroke patients. The earliest and most prevalent pathophysiological hypothesis of increased risk of PSD linked this disorder with left-sided anterior brain lesions (39, 40). However, the significance of stroke lesion location for the consequent appearance of depression has been disputed by several authors (41, 42).

A recent meta-analytical study by Narushima et al. (43) aimed at reappraising the original localization hypothesis found, at 6 months follow-up, a moderately strong inverse correlation between the severity of depressive symptoms and the distance of the anterior border of the left hemisphere lesion from the frontal pole. These authors also hypothesize that the correlation between the proximity of the lesion to the frontal pole and the severity of depressive symptoms may be due to anterior lesions interrupting ascending noradrenergic and serotonergic fibers closer to their origin from the brainstem causing greater depletion of these neurotransmitters than more posterior lesions.

Relationship with Cognitive and Social Impairment

Dementia is frequently observed after stroke (44–46). As many as one third of stroke survivors assessed during hospitalization were found to meet criteria for dementia at a four-year follow-up assessment (47). Additionally, cognitive performance has been reported to be more prevalent in stroke patients with concurrent major depressive episodes compared to non-depressed stroke patients (48–50), especially after left hemisphere lesions (49). Studies are needed to further delineate the temporal relationship between conditions predisposing to dementia and post-stroke cognitive function.

However, the association between depression and cognitive impairment in stroke was found to decline with time. House et al. failed to show significance at 1-year (51) and 2-year follow-ups (52). Furthermore, during the course of a recent double-blind treatment trial with nortriptyline by Kimura et al. (53), patients whose mood disorders remitted exhibited significantly greater recovery in cognitive function compared to patients whose mood disorders did not remit.

Relationship with Functional Impairment and Recovery

Patients affected by stroke manifest a high prevalence of sensory-motor impairment (54, 55). Approximately 80% of patients with acute stroke present with focal weakness or paralysis. The relationship between PSD and functional impairment is complex. The measurement of physical impairment involves an evaluation of motor and sensory functions and of deficits in the performance of activities of daily living (ADL) (18). In a large population of PSD patients, a significant correlation was found between the severity of depressive symptoms and the severity of impairment in ADL (e.g., patients' ability of dress and feed themselves, walk, read and maintain sphincter control) (56). However, a recent study by Nannetti et al. (57) of 117 acute stroke patients selected in an intensive rehabilitation unit failed to show a negative impact of PSD on functional recovery.

Although most stroke patients experience some natural recovery of their neurologic function and ability to perform ADL, at 3 and 6 month follow-ups, patients with depression after stroke were significantly more impaired in their ADL than patients without depression. Moreover, in-hospital ADL impairment was found to correlate with severity of depression (18), suggesting that depression influences ADL recovery.

Chemerinski et al. (58) examined the effect of remission of PSD on ADL recovery. Patients with PSD were selected and randomly assigned to either active treatment with the antidepressant nortriptyline or with placebo. Patients whose depressive disorders remitted during the medication trial had significantly greater recovery in ADL functions, compared with patients whose depression failed to remit.

Treatment

Despite multiple reports on the negative impact of depression on functional post-stroke recovery and prognosis, many patients with PSD do not receive adequate treatment. Physician reluctance to prescribe antidepressants to post-stroke patients may include the belief that depression is an understandable and expectable emotional reaction to the physical impairment of stroke as well as the fear of the potential side effects of psychotropic medications in this mostly elderly patient population.

In the earliest double-blind, placebo-controlled study that examined the efficacy of antidepressant mediation in PSD, patients given nortriptyline showed a significantly greater improvement in various measures of depressive symptoms (i.e., the Ham-D, the Zung Self-Rating Depression Scale, and the profile of depressive symptoms assessed by the Present State Exam) than placebo-treated subjects (59). This study also reported that patients who received active treatment for 6 weeks had significantly lower depression scores that patients who were treated for 4 weeks, suggesting that longer duration of treatment may improve outcome. In later studies, agents such as trazodone (60) and selective serotonin reuptake inhibitors (SSRIs) [i.e., citalopram (61), sertraline (62), fluoxetine (63)] have also shown to be effective treatments for PSD. For example, PSD patients daily treated with 20 mg of fluoxetine showed a higher reduction of Montgomery-Asberg Depression Scores (MADRS) compared to placebo-treated patients (63). In contrast, a study by Robinson et al. (64) failed to show significant differences between PSD patients treated with fluoxetine vs. those treated with placebo.

Besides antidepressant medication, other treatment modalities such as methylphenidate (65), electroconvulsive therapy (66) and repetitive transcranial magnetic stimulation (67) have also been shown to be effective in PSD

Post-stroke Anxiety Disorder

Diagnosis and Prevalence

The DSM-IV-TR criteria for primary generalized anxiety disorder (GAD) include the presence of a sustained worrying state associated with at least three anxiety symptoms, including restlessness, decreased energy, concentration difficulties, irritability, muscle tension, and sleep disturbance, for a period of at least 6 months. The DSM-IV-TR characterizes post-stroke generalized anxiety disorder as "anxiety disorder due to stroke, with generalized anxiety."

As with PSD, differences in selection of patient populations, diagnostic criteria, and time elapsed since stroke account for the variability in reported prevalence rates of post-stroke anxiety disorders by different studies. For example, Leppavuori et al. (68) found, in a study of 277 patients studied at 3–4 months after ischemic stroke, that the frequency of GAD was 20.6%, while a study by Castillo et al. (8) reported that the mean prevalence of GAD in a group of 309 patients hospitalized with an acute stroke was 27%. Moreover, these authors also reported that 75% of those patients who met DSM-III-R criteria for GAD (except for the 6-month duration) also met criteria for major or minor depression, suggesting that post-stroke anxiety disorder and PSD are comorbid conditions.

Anatomical Correlates

A study by Castillo et al. (69) reported that left-hemisphere strokes were associated with comorbid anxiety/depression disorders while right-hemisphere strokes were correlated with pure anxiety disorders. Similar findings were found in a longitudinal study by Astrom (6). In this study, patients with post-stroke GAD also exhibited, at a 3-year follow-up assessment, generalized cerebral cortical and subcortical atrophy. The author hypothesized that this atrophy might play a role in the pervasive nature of post-stroke anxiety though aging, preexisting Alzheimer's disease, chronic decreased cerebral blood flow; comorbid conditions would also need to be considered and ruled out.

Treatment

Since the treatment of post-stroke anxiety disorder has never been systematically studied, at the present time results from studies of patients with anxiety without brain lesions are the only available source of information for the treatment of this disorder.

Benzodiazepine medication is the most commonly employed treatment for anxiety. However, in this mostly elderly population long-acting benzodiazepines can be associated with significant side effects. Due to their more tolerable side effect profile, buspirone and SSRIs might constitute an alternative treatment option (69).

Post-stroke Mania

The concept of secondary mania refers to the occurrence of manic symptoms resulting from neurological, metabolic or toxic disorders (70). Patients with secondary mania showed similar frequencies of insomnia, elation, pressured speech, flight of ideas, and grandiosity when compared to patients suffering from a primary mood disorder (71, 72). While PSD has been the focus of considerable research, because of its relatively rare occurrence, post-stroke mania has rarely been studied (73). In a series of 700 consecutive stroke patients, Starkstein et al. (9) identified only 3 cases of post-stroke mania. Similarly, among 661 stroke patients, Dunne et al. (10) only identified 3 cases with this disorder. Moreover, no patients were found to suffer from post-stroke mania in two large community studies that examined the prevalence of neuropsychiatric disorders after stroke, the Oxfordshire Community Stroke Project (3) and the Perth Community Stroke Study (35).

Clinical, demographic and prognostic features have been difficult to identify in post-stroke mania due to its low prevalence. However, family history of mood disorder was found to be correlated with this disorder (74). Furthermore, Cummings and Mendez (75) reported a significant correlation of post-stroke mania with right hemispheric lesions leading to dysfunction of the ventral limbic circuit involving the orbitofrontal and basotemporal cortex as well as the caudate and dorsomedial thalamic nucleus. The authors hypothesized that, in contrast with PSD, post-stroke mania may be rare because dysfunction in more than one area (i.e., limbic lesion and subcortical atrophy) of the right hemisphere is required for its production.

Lithium has been the most commonly used treatment for secondary mania. However, since the results published in the literature involve only individual case reports and open label treatment studies, there is no clear evidence currently regarding the most effective treatment for post-stroke mania.

Other Post-stroke Neuropsychiatric Disorders

Besides the post-stroke psychiatric disorders described above, other conditions such as catastrophic reaction, anosognosia, pseudobulbar affect, psychosis, and abulia can also be observed in stroke patients.

Catastrophic Reaction

"Catastrophic reaction" is a term created by Goldstein in 1939 (76) to describe a series of symptoms including aggressiveness, anxiety, tearfulness and renouncement occurring in patients with brain insults who are unable to cope with their physical or cognitive impairments. These emotional outbursts are believed to be short lived and related to trigger stressors such as performing a cognitive task during a neuropsychological assessment.

Results from a study by Gainotti (77, 78) suggested that in stroke patients, catastrophic reaction (CR) is associated with left hemisphere brain damage. This author also hypothesized that many patients who exhibit tearfulness and depression triggered by the stress of psychiatric examinations are usually diagnosed as having PSD; however, rather than having a prolonged depressive disorder, they may be having a brief CR.

Starkstein et al. (79) developed a CR scale to examine the frequency of this disorder and its relationship with depression. In this study the frequency of major depression was reported to be significantly greater in stroke patients with CR. Moreover, these patients also had significantly higher Hamilton anxiety scale scores and greater impairment in activities of daily living than patients without CR. However, patients with CR did not show significantly more cognitive impairment than those without this disorder.

Anosognosia

Anosognosia is a term coined by Babinski (80) to describe patients with cerebral lesions who ignore their hemiplegia. Currently, this term is used also to characterize patients with lack of awareness of other deficits (e.g., amnesia and visual loss) resulting from any brain disorder (81).

A meta-analysis by Pia et al. (82) found that the probability of developing anosognosia is highest when the stroke lesion involves both parietal and frontal structures. Moreover, in a study of patients with stroke, those who exhibited anosognosia showed significantly higher rates of hemineglect, disturbances in prosody and deficits in recognizing facial emotions (83).

Pathological Affect

Pseudobulbar affect describes uncontrollable episodes of laughing and crying induced by corticobulbar or corticopontine lesions resulting from bilateral strokes. Since it was later recognized that in most cases these symptoms were not associated with bilateral upper motor neuron lesions, the term pseudobulbar affect was replaced with the more general term pathological affect. Thus, pathological affect is an affective disinhibition syndrome characterized by uncontrollable episodes of laughter or crying that are discordant or disproportionate to the situation at hand (84). Besides strokes, this disorder has been frequently reported in demyelinating diseases (85), and amyotrophic lateral sclerosis (86). The reported prevalence rates of this disorder following strokes vary from 11–52% (86).

In a study by Robinson et al. (88) of 28 patients with either acute or chronic stroke, patients treated with nortriptyline for 4–6 weeks showed significantly greater improvement in pathological affect as measured by the Pathological Laughter and Crying Scale (PLACS) when compared with placebo-treated controls. Moreover, in another double-blind drug trial using a crossover design, Andersen et al. (89) reported that patients treated with citalopram responded to treatment, with a reduction in the number of crying episodes by at least 50%.

Post-stroke Psychosis

Psychotic symptoms (i.e., delusions and hallucinations) are rarely observed after stroke. A 9-year follow-up longitudinal study of stroke patients only found five patients who exhibited psychotic symptoms. Moreover, since all of these patients had right frontoparietal lesions and, when compared to stroke patients without psychosis, showed higher frequency of subcortical atrophy (90), the authors hypothesized that these structural findings are risk factors for developing psychosis after stroke.

Levin and Finklestein (91) found, in 8 patients without earlier psychiatric disorder, delayed psychotic symptoms (i.e., delusions, hallucinations) up to 11 years after right temporoparietooccipital stroke. Seven of these patients had clinical seizures in close temporal relationship to the psychosis, and a significant improvement of psychotic symptoms was observed after administration of antiepileptic drugs, but nonconvulsive status was not ruled out in any of these cases.

Post-stroke Apathy

The apathy syndrome is a simultaneous decrease in the behavioral, cognitive and emotional concomitants of goal-directed behavior due to loss of motivation, clinically evidenced by symptoms such as flat affect as well as decreased interest and poor effort in everyday activities (92).

In a study of 80 acute stroke patients by Starkstein et al. (14) apathy alone was exhibited by 11% of patients while another 11% displayed both apathy and depression. However, a study by Brodaty et al. (15) found that the rate of apathy in a cohort of 167 patients assessed at 3 – 6 months post-stroke was 26.7%. The variability in the methods used to assess apathy might explain the profound differences in the reported rates of this disorder after strokes (15).

A significant inconsistency also exists with respect to the association between apathy and stroke lesion location, with reports of left (93), right (77) and bilateral (94) cerebral dysfunctions.

Multiple factors such as advanced age, deficits in ADL (14), lower global cognitive function (14, 95), poor verbal fluency (94, 95), reduced attention and speed of information processing (15) have been reported to be correlated with apathy after stoke.

Conclusion

This review has examined a few of the numerous neuropsychiatric disorders that may occur after stroke. Depression and anxiety, the two most common of these disorders, have been shown to be associated with particular lesion locations and to adversely affect the physical recovery from cerebrovascular lesions. On the other hand, depression has been shown to respond to treatment with antidepressant medication. Since the effective treatment of post-stroke neuropsychiatric disorders have the potential for improving the outcome and quality of life of stroke survivors, additional studies are needed to elucidate the course, mechanism, and effective treatment of these disorders.

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Hyoid Bone Fractures

Elie Levine, M.D., and Peter J. Taub, M.D.

Abstract

Surgeons who manage patients with craniofacial trauma should be comfortable with evaluating and treating fractures throughout the head and neck. This includes the hyoid bone, which may cause significant airway concerns if fractured. The authors report the case of a patient who sustained a fracture of the hyoid bone. The hospital records from a busy, level I trauma center were reviewed to document similar injuries over a seven-year period. To supplement the scant literature concerning hyoid fractures, a review of the anatomy, diagnosis, and management of such injuries is provided.

Key Words: Craniofacial trauma.

Introduction

A basic knowledge concerning fractures involving the neck is important for surgeons who are involved in the evaluation and management of patients with fractures of the craniofacial skeleton. This includes the anterior neck as well as the posterior cervical spine. The incidence of concomitant cervical spine injury with facial trauma approaches 10% (1). The incidence of hyoid bone injuries is much lower and therefore sparsely described in the literature. The authors present the case report of a trauma patient with a fracture of the mandible, whose preoperative CT scan identified an associated fracture of the hyoid bone. The records of a major level I trauma service were subsequently examined using the global International Statistical Classification of Diseases, 9th Revision (ICD-9) code for hyoid fracture. Patients who had laryngeal, tracheal, or cricothyroid cartilage injury, which are included in the same ICD-9 code, were excluded. Finally, the anatomy and management of hyoid bone fractures was reviewed.

Case Report

A 50-year-old male was transferred from another institution following a motor vehicle accident in which he was a restrained driver. His medical history was significant for a seizure disorder for which he was taking anti-seizure medication. On examination, he was noted to have multiple small abrasions over the face and tenderness over the left mandible. His neck was supple without edema or ecchymosis, and the trachea was in the midline. There was no appreciable tenderness over the cervical spine; however, he did complain of anterior neck "discomfort." The patient had no dysphagia, odynophagia, trismus, or stridor. On intraoral examination, he was noted to be edentulous with no mucosal lacerations. There was a minimal amount of ecchymosis in the gingivobuccal sulcus on the left lower quadrant of the oral cavity. Following transfer, he underwent emergent exploratory laparotomy and repair of gastric perforations.

A CT scan of the head and neck was performed, with 2 mm slices in the axial and coronal planes. The findings demonstrated a comminuted fracture of the left side of the mandible and the right side of the hyoid (Fig. 1). The former extended to just below the level of the coronoid process and was comminuted in the region of the mandibular angle.

The patient underwent laryngoscopy that demonstrated mobile but edematous vocal folds and arytenoids, an unrelated 3 mm polypoid lesion arising posteriorly and a right vocal process granuloma. In addition, the patient had a normal contrast swallow study.

He eventually underwent open reduction and internal fixation of the mandibular fracture without incident and was extubated at the conclusion of the procedure. He has since been seen for follow-up at 6 and 12 months postoperatively, with no adverse sequelae.

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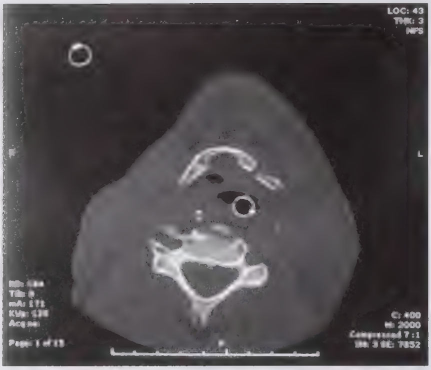

Fig. 1. CT scan demonstrating fracture of the hyoid bone.

Chart Review

The medical records from a busy, level I trauma center over a seven-year period were reviewed. In this span, 2,235 patients with fractures of the craniofacial skeleton were identified and treated. A total of eight patients were discharged with an ICD-9 code of 807.5 or 807.6. This code covers fractures of the larynx and trachea, closed or open. Included within this code are fractures of the hyoid bone, thyroid cartilage, and trachea. Of the eight charts reviewed, only the patient described above had an associated fracture of the hyoid bone. Two patients had fractures of the larynx, two patients had fractures of the thyroid cartilage, and one patient had a fracture of the cricothyroid cartilage.

Discussion

Anatomy

The hyoid bone (Fig. 2) is a U-shaped bone in the anterior neck. Its name is derived from the Greek word *hyoeides* meaning "shaped like the letter upsilon." It lies at the level of the C_3 vertebra in the angle between the thyroid cartilage and the mandible and consists of three segments: the central body of the hyoid, the lesser horns, and the greater horns. The greater horns project posterosuperiorly and laterally from the body, and the lesser horns project superiorly at the junction of the body and the greater horns. It is suspended by the musculature that connects the mandible, styloid process, thyroid cartilage, manubrium, and scapulae. The hyoid bone, which does not articulate with any other bones, is connected to the styloid processes by the stylohyoid ligaments.

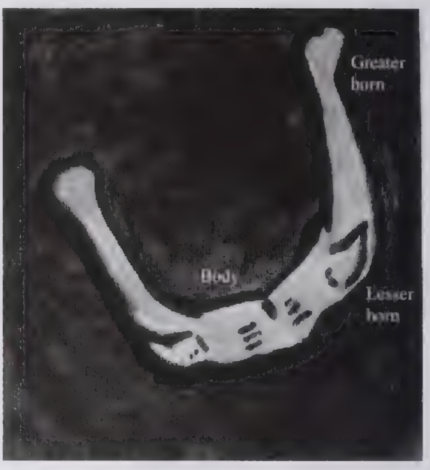

Fig. 2. Anatomy of the hyoid bone.

Because the hyoid bone is free-floating, its physiologic function is based on its surrounding muscles and muscular attachments. The musculature attached to the hyoid in the anteriolateral neck can be divided into suprahyoid muscles and infrahyoid muscles (Fig. 3).

The suprahyoid muscles consist of the stylohyoid, geniohyoid, mylohyoid, and digastric muscles, and connect the hyoid to the cranium. The mylohyoid originates from the mylohyoid line of the mandible and inserts on the raphe and body of the hyoid bone. It functions to elevate the floor of the mouth, the hyoid bone, and the tongue during speech and swallowing. The stylohyoid muscle originates from the styloid process and inserts onto the body of the hyoid bone. It functions to elevate and retract the hyoid bone, resulting in elongation of the floor of the mouth. The geniohyoid muscle originates from the inferior mental spine of the mandible and inserts on the body of the hyoid bone. It pulls the hyoid bone anteriorly and superiorly, widens the pharynx and helps shorten the floor of the mouth. The anterior belly of the digastric muscle originates from the digastric fossa of the mandible, and the posterior belly originates from the mastoid notch of the temporal bone. Both of these muscles insert onto the body and greater horn of the hyoid and function to depress the mandible depression, raise the hyoid, and stabilize the hyoid during speech and swallowing.

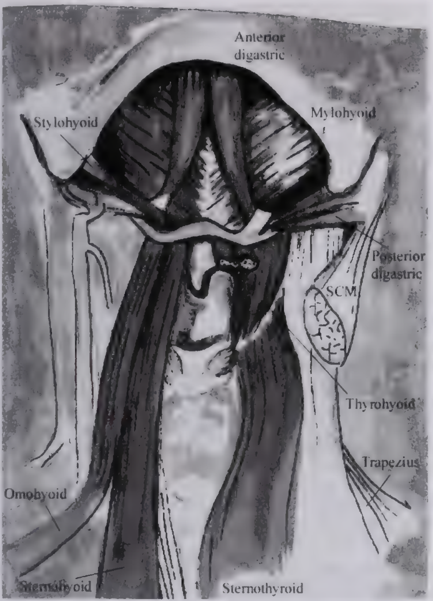

Fig. 3. Schematic drawing demonstrating the relationship of the hyoid bone to the suprahyoid and infrahyoid muscles.

The infrahyoid muscles, also known as the strap muscles, lie below the hyoid bone. This group consists of four muscles that interconnect the hyoid bone to the sternum, clavicle, and scapula. They also work in connection with the suprahyoid muscles to provide a stable base for the tongue. They include a superficial group (sternohyoid and omohyoid) and a deep group (sternothyroid and the thyrohyoid). The sternohyoid muscle originates from the manubrium and the medial aspect of the clavicle and inserts onto the body of the hyoid. It functions to depress the hyoid following elevation during swallowing. The omohyoid muscle originates from the scapula near the suprascapular notch and inserts onto the inferior aspect of the hyoid. It serves to depress and retract the hyoid. The sternothyroid muscle also serves to depress the hyoid as well as the larynx. It originates from the posterior aspect of the manubrium and inserts onto the thyroid cartilage. The thyrohyoid muscle originates from the oblique line of the thyroid cartilage and inserts onto the inferior aspects of the body and greater horn of the hyoid. It serves to depress the hyoid and elevate the larynx.

Classifications

In 1961 Weintraub (2) studied fractures of the hyoid bone and classified them into those due to inward compression, those due to anterior-posterior compression, and avulsion type injuries. Lakhia et al. (3), on the other hand, classified hyoid bone fractures by location. Fractures may occur in the body, the lesser horn, and the greater horn. Furthermore, closed fractures may be displaced inward or outward, and open and compound fractures may be externally displaced or displaced into the pharynx, which often results in crepitus.

Diagnosis

The most common cause of hyoid bone fractures today is motor vehicle trauma (4, 5). (In the past, strangulation and hanging caused a majority of cases [2]). While fractures of the craniofacial skeleton and cervical spine are relatively common, fractures of the hyoid bone are quite rare, accounting for 0.002% of all fractures (6, 7). Hyoid bone fractures often occur with concomitant mandible fractures, thyroid cartilage fractures, and cricoid cartilage fractures. The low number of hyoid injuries is believed to be due to the protective effect of the mandibular position and the free-floating nature of the hyoid bone, with its mobility in all directions (3, 8). Fewer than 30 cases of hyoid bone fractures have been reported in the literature.

The diagnosis of hyoid bone fracture is difficult. Usually, the finding is made by CT scan of the head and neck. Plain radiographs may reveal hyoid bone fractures; however, the detailed anatomy of the hyoid bone is often obstructed by the patient's mandible or soft tissue. Fractures typically occur through one of two mechanisms: (a) They may result from direct blows to the hyoid. This typically occurs when the neck is extended, exposed, and unprotected by the mandible. (b) The hyoid bone can be fractured as an avulsion injury secondary to sudden neck hyperextension or forced swallowing. Both mechanisms may occur during motor vehicle accidents, whether the patient is restrained or unrestrained.

The patient may present with ecchymosis of the neck, edema, crepitus, or stridor (4, 9, 10). Patients may complain of anterior neck pain, decreased range of motion, dysphonia (nasal or raspy sound), dyspnea, dysphagia (typically of solid foods), persistent cough, painful coughing, pain with nose blowing, or gagging (3, 4, 11, 12). In more severe injuries, patients may complain of respiratory distress or hemoptysis (4, 12, 13).

Management

A consensus regarding the management of hyoid bone fractures does not exist (3). Closed fractures of the hyoid are often uncomplicated and may be managed conservatively with admission to the hospital for a short period of observation and possibly intravenous steroids in tapering doses (7, 14). Analgesics, restriction of movement and a soft diet are also useful. Pharyngolaryngoscopy is required to assess active and passive mobility of the vocal cords.

Surgical intervention for hyoid bone fractures is usually restricted to patients with airway compromise, pharyngeal perforations and painful symptoms that do not respond to conservative care. Emergent treatment of airway compromise is rarely needed; however, it may be required shortly after the injury or in a delayed manner (9, 15 – 17). Severe comminuted, open fractures may necessitate neck explorations, debridement and stabilization or removal of parts or all of the hyoid bone. The case reported by Lakhia et al. (3), had symptoms that did not resolve with conservative care and required open reduction and fixation with tension band wiring. Removal of all or part of the hyoid bone typically occurs in the case of hyoid bone fractures with sharp ends that threaten surrounding soft tissue structures. Removal of the entire hyoid bone rarely effects deglutition.

Conclusion

The authors report one case of hyoid bone fracture over a seven-year period at a busy regional trauma center, confirming that fractures of the hyoid bone are rare injuries. The diagnosis of such fractures is clinically difficult and often requires CT imaging for conclusive diagnosis. While most of these injuries can be managed conservatively, one must remain clinically vigilant to prevent airway compromise and potentially catastrophic consequences.

Acknowledgment

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Laparoscopic Enucleation of Mesenteric Cyst:

A Case Report

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Abstract

Intra-abdominal lesions, such as mesenteric cysts, are uncommon disorders. Most are discovered incidentally during routine abdominal examinations. They generally do not show typical clinical findings. Laparoscopic surgery has been used to remove a wide variety of mesenteric cysts. We report a patient with a mesenteric cyst, who was treated by laparoscopic enucleation.

Key Words: Mesenteric cyst, laparoscopic enucleation.

Introduction

MESENTERIC CYSTS are rarely seen intra-abdminal lesions. The average incidence of these lesions is approximately 1:100,000 in adults, 1:20,000 in children (1, 2). They can be uni- or multilocular, and are mostly benign. Approximately 830 cases have been reported in the literature and only four of them were found to be malignant (1 – 5).

Although mesenteric cysts are usually diagnosed during routine abdominal examinations, they can present with various signs, such as acute abdominal pain, chronic abdominal pain, nausea and vomiting, or change in bowel habit. Although rare, shock due to rupture or bleeding of the cyst, intestinal obstruction secondary to external compression and volvulus or torsion of the cyst have been reported (1 – 3).

Case Report

A 74-year-old woman was admitted to our department with non-localized abdominal pain and constipation during the previous year. Physical examination did not show any abnormality other than a median incision scar on the lower abdomen from a hysterectomy which she had had for myoma 15 years ago. All laboratory tests, including malignancy parameters, were within normal limits.

Abdominal ultrasonography showed a cyst 5 cm in diameter at the mesentery of the ileum on the right lower quadrant. The nature of the cyst was homogeneous with low internal echo. Computed tomography (CT) showed the cyst to be circumscribed and unilocular with a thin capsule, located at the mesenterium of the ileum (Figure).

Three trocars were used: a 10 mm trocar was placed at the midline, 2 cm above the umblicus, using an open technique; a 5 mm trocar was placed lateral to the left rectus abdominus muscle at the left upper quadrant; and a second 5 mm trocar was placed lateral to the left rectus abdominus muscle

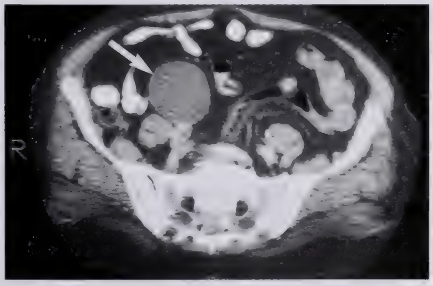

Figure. Abdominal computed tomography shows a unilocular (arrow), well-circumscribed cyst with a thin capsule, located in the mesenterium of the ileum.

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in the left lower quadrant. During exploration, the cyst was seen at the distal ileum mesentery. It was attached to mesenterium by its posterior wall, and the lateral and anterior walls were free of any attachment. Initially, the cyst was dissected from the mesenterium by blunt and sharp dissection. After the cystectomy was completed, it was put into an endobag. The cyst contents were aspirated within the endobag and the cyst was then withdrawn with the endobag through the 10 mm trocar site. Histopathological examination revealed a 1 mm thick fibrous wall with cuboidal lining cells, which was diagnosed as a simple mesothelial cyst according to de Perrot classification (Table).

The patient was discharged on the first postoperative day. She is doing well, with no complaints for 16 months.

Discussion

Mesenteric cysts are uncommon intra-abdominal disorders that do not show typical clinical findings. Almost half of the cases are noticed incidentally in routine abdominal examination, when the patients present with the various abdominal complaints. Mesenteric cysts are most frequently located in mesentery of the small bowel; however, they can also be found in mesentery from the jejunum to the rectum. Ultrasonography and CT are valuable diagnostic tools in this process. CT is useful for delineating the location, extent and nature of these lesions (1–3).

TABLE

de Perrot Classification of Mesenteric Cysts

Origin	Type
1. Cysts of lymphatic origin	a. Simple lymphatic cyst b. Lymphangioma
2. Cysts of mesothelial origin	a. Simple mesothelial cyst b. Benign cystic mesothelioma c. Malignant cystic mesothelioma
3. Cysts of enteric origin	a. Enteric duplication cyst b. Enteric cyst
4. Cysts of urogenital origin	
5. Mature cystic teratoma	Dermoid cyst
6. Nonpancreatic pseudocysts	a. Traumatic origin b. Infectious origin

Adapted with permission from de Perrot M, Bründler MA, Tötsch M, et al. Mesenteric cysts. Toward less confusion? Dig Surg 2000; 17(4):323–328 (1).

The first report of a mesenteric cyst case was in an autopsy by an Italian anatomist, Benevenni, in 1507. The first description of a chylous mesenteric cyst was recorded by Rokitansky in 1842. The first successful surgical resection was performed by Tillaux in 1880 and the first successful laparoscopic resection was reported by Mackenzie (1, 2).

The etiology of lymphangiomas and benign cystic mesotheliomas has not been defined clearly. However, simple lymphatic and mesothelial cysts are mostly congenital. They can also be related to previous pelvic surgery, trauma, pelvic inflammatory disease, endometriosis and neoplasia (1, 2). Our patient had a hysterectomy 15 years previously, which may be a reason for her cyst.

Mesenteric cysts should be treated when they become symptomatic or when they cause complications. Surgery can prevent complications, such as rupture, bleeding, intestinal obstruction, volvulus, torsion and infection. Treatment options for mesenteric cyst are simple drainage, external or internal excision, enucleation, and external or internal marsupialization (1–3, 6). The mainstay of treatment is surgical removal of the cyst. Acceptable therapy of the mesenteric cyst is complete resection to avoid malignant transformation (1, 3, 5). Excision of the cyst with segmental resection of involved bowel may be required in some patients (1, 2).

Currently, with the developments in laparoscopic surgery, complete laparoscopic cyst enucleation can be performed without any complications in appropriately selected patients.

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Propylthiouracil-Related Hemorrhagic Diathesis:

A Case Report and Review of the Literature

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Abstract

We present an unusual case of a drug-related hemorrhagic diathesis. One month prior to admission, the patient was diagnosed at another medical center as having Graves' disease and propylthiouracil therapy (PTU) was initiated. Since clinical recovery was not achieved, the PTU was quickly increased to an unconventional daily dose of 1,000 mg. The patient was referred to our hospital because of spontaneous epistaxis, multiple ecchymoses and prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), which developed soon after the increase in PTU dose. Drug-related hemorrhagic diathesis was considered, after other possible causes had been eliminated. To the best of our knowledge, this is the first reported case of spontaneous hemorrhage due to PTU use.

Key Words: Propylthiouracil, hemorrhagic diathesis, factor deficiency.

Case

A 23-YEAR-OLD WOMAN was admitted to our university hospital because of epistaxis and ecchymoses over multiple areas of her skin, especially on her lower extremities. She had been well until one month earlier, when tremor, tachycardia, heat intolerance, irritability and anxiety developed. A diagnosis of Graves' disease had been established at another hospital, and 300 mg of daily PTU (in three divided doses) was begun. As no notable clinical and laboratory improvements were achieved, the PTU dose was increased to an unconventional dose, 1,000 mg daily (in five divided doses). After a few days epistaxis developed, and the patient reported the passage of tarry stools. On physical examination at our hospital, she appeared anxious, was tachycardic (120 beats/minute) but afebrile at 36.4°C, and had blood pressure of 120/80 mm Hg in both arms. Multiple ecchymoses and petechiae were seen on her abdomen, lower extremities and back. Heart sounds were distant and lungs were clear on auscultation. The extremities and abdomen were normal, except for the ecchymoses. A complete blood count revealed a hemoglobin level of 12.8 g per liter with a mean corpuscular volume (MCV) of 82.4 μm^3, a white cell count of 8,860 cells/mm^3 and a platelet count of 505,000 cells/mm^3. Serum levels of electrolytes, creatinine, blood urea nitrogen, albumin, total protein, calcium and bilirubin were normal, as were the results of liver-function tests and urinalysis. A chest radiograph and ultrasound of the abdomen were both normal. An electrocardiogram revealed sinus tachycardia at a rate of 120 beats/min with no ischemic findings. The admission PT and aPTT were 195 and 102 seconds, respectively. Bleeding and clotting times were within normal ranges. Drug-related hemorrhagic diathesis was considered as a cause of the abnormal findings.

Discussion

When a bleeding patient presents with substantially prolonged PT and aPTT and normal platelet counts, certain causes should be considered. These causes, as listed in Table 1 (1), were not compatible with this patient's presentation, since levels of fibrinogen, factor VIII and von Willebrand factor (vWF) were normal and the pa-

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TABLE 1
Reasons for Prolongation of Both PT and aPTT with a Normal Platelet Count

Bleeding	No Bleeding
Afibrinogenemia	Hypofibrinogenemia
Severe deficiencies of factors II, V and X	Mild deficiencies of factors II, V and X
Combined factors V and VIII deficiency	
Combined deficiency of the vitamin K-dependent factors	
Acquired inhibitors to factors II and V	
Acquired factor X deficiency	

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tient had no history of inappropriate or prolonged bleeding.

A tendency towards bleeding has been reported among patients using thionamide drugs. However, this tendency is rare and has only been observed in patients undergoing surgical interventions. On the other hand, coagulation studies of our patient revealed a very severe deficiency of all vitamin K-dependent factors (Table 2). In the reported cases, decreased levels of prothrombin were thought to be responsible for the bleeding (2, 3). However, no hemorrhagic diathesis has been reported among patients using thionamides in the absence of surgical trauma. In the literature, several cases of bleeding diathesis and thrombocytopenia, attributed to PTU use, have been reported (4). In our case, the thrombocyte count was normal.

PTU-associated vasculitis has been reported in a few cases (5–7). More specifically, well-defined, PTU-induced, small vessel vasculitis and alveolar hemorrhages, which are associated with antineutrophil cytoplasmic antibody (ANCA) development, have been reported (8, 9). However, by history, on physical examination and according to the laboratory data, our patient had no features consistent with vasculitis.

As mentioned above, our patient had no history of bleeding and her family history was unremarkable. She had not used any drugs prior to her intake of PTU. She had had a normal PT and aPTT on routine testing prior to treatment at the previous

TABLE 2
Hematological Laboratory Values

Variable	Admission	Day 1	Day 2	Day 6	On Discharge (Day 12)
Hematocrit (%)	36				35
WBC (cells/mm^3)	8,680				7,680
Platelet (cells/mm^3)	505,000				393,000
Thyroid functions*					
(TSH, T3, T4)	(0.11; 5.17; 3.43)			(0.027; 4.32; 2.08)	
D-dimer (μg/dL)#	0.22			0.22	
Fibrinogen (mg/dL)¶	408			484	
ANA (anti-nuclear Ab)	Negative				
P-ANCA	Negative				
C-ANCA	Negative				
Antiphospolipid ab. IgG	Negative				
Antiphospolipid ab. IgM	Negative				
Bleeding time (Ivy) (min)ƒ	4.2				
vWF£	160				
AT III (%)≠	112				
Prothrombin	1				83
Factor VII (%)€	15				90
Factor VIII (%)€	113				110
Factor IX (%)€	10				80
Factor X (%)€	17				95
PT (sec)∫	195	46.5	41.4	39.2	18
aPTT (sec)∫	102	69.4	54.4	56	36
CRP (mg/dL)	12.4				

CRP = C-reactive protein, WBC = white blood cells, AT = antithrombin, C-ANCA=cytoplasmic antineutrophil cytoplamic antibody, P-ANCA = perinuclear antineutrophil cytoplasmic antibodies.

Normal ranges: *TSH (0.27–4.2), fT4 (0.93–1.7), fT3 (1.8–4.6); #D-dimer (0–0.4); ¶Fibrinogen (200–400); ƒBleeding time (3–6); £vWF (50–160); ≠AT III (80–120), €Factor II-VII-VIII-IX-X (60–150); ∫PT (11–14.2), aPTT (26–37.2).

medical center and during a routine laboratory examination performed one year earlier. When we stopped the PTU and administered vitamin K, the patient's levels of prothrombin and of factors VII, IX and X normalized within 12 days (Table 2). In view of this, we concluded that high-dose PTU had caused an inhibition of vitamin K and, consequently, of vitamin-K-dependent coagulation factors. Subsequently, she was treated with a 200 mg daily dose of methimazole, while monitored closely. Fortunately, no further complications occurred.

One might argue that the elevation in factor levels was due to administration of fresh frozen plasma. However, we only infused four units of fresh frozen plasma (FFP) on admission, along with one dose of vitamin K after evaluating the patient. Four units of FFP would not be expected to cause such a dramatic increase in factor levels. During a follow-up visit one month after discharge, and while the patient was still on 200 mg of methimazole daily, all her factor levels were still in the normal range.

One question of great interest is whether the hemorrhagic diathesis we observed is a dose-dependent effect. In our patient, no hemorrhagic diathesis had occurred while she was receiving 300 mg of PTU prior to admission, or while she was on methimazole following discharge. Thionamide drugs (propylthiouracil and methimazole) resemble the methyltetrazole-thiol leaving group of certain cephalosporin antibiotics, and both thionamides and cephalosporins have been found to inhibit the vitamin-K-dependent gamma-carboxylation of glutamic acid *in vitro* (2). Probably, mild clotting factor deficiencies due to inhibition of this step occur in many patients, though this remains subclinical at regular doses. The important point here is that higher doses of thionamide drugs might cause hemorrhagic diathesis, especially in patients taking oral anticoagulants and in patients who already have a tendency to bleed due to idiopathic thrombocytopenic purpura or other predisposing conditions.

Conclusions

This presented case is unusual and warrants reporting for several reasons. First, to the best of our knowledge, spontaneous hemorrhage while on PTU, in the absence of trauma or surgical interventions, has not been reported previously in the literature. Second, although thrombocytopenia associated with PTU usage has been reported, no clotting factor deficiencies have been reported until now. Moreover, deficiency of vitamin-K-dependent coagulation factors due to PTU use has only been demonstrated in cats, not in humans. Hence, to our knowledge, this is the first case of a human patient on high-dose PTU exhibiting vitamin-K-dependent factor deficiency.

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Increased Circulatory MMP-2 and MMP-9 Levels and Activities in Patients with Type 1 Diabetes Mellitus

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Abstract

Background: Type 1 diabetes mellitus (T1DM) is an autoimmune disorder of unknown etiology. It has been suggested that metalloproteinases (MMPs) play important roles in the development and complications of autoimmune disorders. This article presents our research on the expression or activities of MMPs in Taiwanese T1DM patients.

Methods: Levels and activities of plasma MMP-2 and MMP-9 in patients with T1DM were investigated and compared to those of control individuals by enzyme-linked immunosorbent assay and zymography.

Results: Circulatory levels and activities of MMP-2 and MMP-9 in patients with T1DM were significantly higher than those in control subjects.

Conclusions: MMP expression and activities are significantly increased in patients with T1DM. Our results not only document plasma MMPs levels and activities in the Taiwanese population (with a very low type 1 diabetic incidence), but also suggest that MMP expression and activity are elevated before the onset of complications in diabetic patients.

Key Words: Matrix metalloproteinase-2, matrix metalloproteinase-9, type 1 diabetes mellitus, diabetes.

Introduction

TYPE 1 DIABETES MELLITUS is a metabolic disease that exhibits hyperglycemia due to an inability to secrete insulin. The disease process is believed to be due to an autoimmune response that causes selective destruction of insulin-secreting islet β-cells. Clinical manifestations of T1DM include very low insulin secretion, absolute requirement for exogenous insulin, low age of onset, and high prevalence of autoantibodies directed against antigenic determinants of the β-cells. The incidence of T1DM is much lower among Taiwanese than among Caucasians (1). The average annual incidence of T1DM in Taipei is approximately 1.5 per 100,000 (1). Taiwanese and Caucasoid patients with T1DM display different clinical manifestations, such as the prevalence of different autoantibodies and genetic traits (2, 3). Therefore, it is likely that several genetic and environmental factors contribute to the autoimmune process in different ethnic groups. A high proportion of T1DM patients of long duration have a tendency to develop diabetic nephropathy with the accumulation of extracellular matrix (ECM) proteins within the renal interstitium and progressive tubular atrophy.

Matrix metalloproteinases are a family of proteolytic enzymes that play crucial roles in normal remodeling of connective tissue and the degradation of basement membrane and surrounding ECM in various physiologic situations. MMPs are also involved in numerous pathological conditions, including atherosclerosis, inflammation, tumor growth and metastasis. Evidence from metabolic studies of experimental animal models demonstrates that enhanced production of collagen is a key event in the development of diabetic glomerular ECM abnormalities. Recently it has been proposed that MMPs participate in the process of concurrent reduced degradation and the enlargement of mesangial area during the pathogenesis of diabetic nephropathy (4–6).

Matrix metalloproteinase-2 (MMP-2) gene downregulation is observed in glomeruli from type 2 diabetic patients (7). An MMP induction and activation system in human arterial vasculature is downregulated in diabetes (8). However, contradictory observations suggest that MMP-2 protein and enzyme activity in kidney samples from diabetic patients are elevated (9). Increased plasma matrix metalloproteinase-9 (MMP-9) activity in the left ventricle of alloxan-induced diabetic wild-type mice is

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also documented (10). In human subjects, circulating MMP-9 levels are increased in type 2 diabetic patients with coronary artery disease, and elevated serum MMP-9 concentrations are linked to premature coronary atherosclerosis (11). It is proposed that increased plasma levels of MMP-9 occur before the development of renal microvascular complications in patients with type 2 diabetic mellitus (12).

Expression and activities of MMPs in diabetes have been studied predominantly in microenvironmental renal and cardiac tissues, with conflicting results. Discrepancies exist among diabetic patients with different ethnic backgrounds, which reveals that ethnicity and environmental factors are involved in the diabetic pathogenesis (13, 14). Therefore, we wanted to determine whether MMP expression or activity is altered in Taiwanese T1DM patients, a population with the lowest range of diabetic incidence (1), and to clarify the reported conflicts as well.

Materials and Methods

Study Subjects

Two hundred and one consecutive T1DM patients attending the diabetic clinic of the Division of Endocrinology and Metabolism, Veterans General Hospital-Taipei, were recruited. The average residual C-peptide level (measured by using the Human C-Peptide RIA kit, Linco Research Inc., St. Charles, MO, USA) of the T1DM patients was 0.13 ± 0.04 nM/L (Table 1). One hundred and eighty-nine healthy control subjects were also recruited from the Physical Check-up Unit, Taichung Veterans General Hospital. Fasting blood samples from all the study subjects were collected from a median cubital vein and drawn into a vacutainer containing 1.8 mg/mL edetic acid (EDTA), then centrifuged within 1 h at 3,000 rpm for 5 min, and the plasma was stored at – 80°C until analysis. The demographic characteristics and clinical manifestations of each patient were filed for statistical analysis (Table 1). Written consent was obtained from all the study subjects after the nature of the procedure was explained. Protocol for this study was reviewed and approved by the Ethics Committee of Hung Kuang University.

Zymographic Analysis of MMP-2 and MMP-9 Activities

MMP-2 and MMP-9 activities were detected using gelatin zymography (15). In brief, ten-fold diluted sera containing 20 μg of total proteins, quantified by the Bio-Rad Protein Assay kit (Bio-Rad Laboratories, Inc., CA, USA), were loaded into each well on 10% gelatin zymography gels. Proteins were initially separated under nonreducing condition at 15 mA through the stacking gel, and the current was increased to 20 mA during the rest of separation. The gels were then rinsed twice in 2.5% Triton X-100 and incubated overnight (16 h) in substrate buffer containing 50 mM Tris-HCl and 5 mM CaCl$_2$. The activated gels were stained by Coomassie blue R-250 followed by destaining in solution containing 55% methanol and 7% acetic acid. Areas of digestion were visualized as non-stained regions of the gel.

TABLE 1

Demographic Characteristics and Biochemical Information on Subjects in This Study

	Study Subjects	
	Control (n=189)	T1DM (n=201)
Sex (M/F)	99/90	85/116
Age (yr)	58.2±10.6	14.4 ± 0.6
Age of onset (yr)	-	9.6 ± 0.5
Duration (yr)	-	4.5 ± 0.2
C-peptide (nM/L)	-	0.13 ± 0.04
BMI (kg/m^2)	24.52±3.40	25.34±3.16
Fasting glucose (70 – 110 mg/dL)*	95.69±6.79	180.38±70.65
Systolic pressure (120 – 140 mm Hg)*	125.42±19.18	135.22±18.19
Diastolic pressure (70 – 90 mm Hg)*	79.20±10.38	79.99±10.51
Blood urea nitrogen (6 – 22 mg/dL)*	15.86±5.09	17.58±8.07
Creatinine (0.6 – 1.4 mg/dL)*	1.11±0.42	1.04±0.44
Cholesterol (125 – 240 mg/dL)*	201.18±37.51	198.02±42.12
HDL-C (>35 mg/dL)*	58.35±13.88	46.52±13.43
TC/HDL-C	3.59±0.90	4.51±1.31
Triglycerides (20 – 200 mg/dL)*	142.54±125.52	184.51±153.74
Uric acid (2.4 – 7.2 mg/dL)*	6.56±1.64	6.12±1.88

*Numbers in parenthesis indicate the normal reference range of each biochemical test.

**Data are presented as mean ± standard deviation.

BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, TC = total cholesterol.

Enzyme-Linked Immunosorbent Assay (ELISA)

Concentrations of MMP-2 and MMP-9 in sera were measured in duplicate using a commercial ELISA kit according to the manufacturer's protocols (R&D Systems Inc., Minneapolis, MN, USA). In brief, 100 μL of MMP-2 or MMP-9 assay diluent was added to each well and then 50 μL of standard or control samples. After 2 h of incubation at room temperature on a constant shaker (500 ± 50 rpm), the reaction solution was aspirated and the wells were washed 4 times with wash buffer; 200 μL of MMP-2 or MMP-9 conjugate was then added to each well and incubated for another 2 hr on the shaker at room temperature. Then the aspiration/wash steps were repeated as mentioned above, followed by adding 200 μL of substrate solution to each well. The microplate was allowed to stand for 30 min at room temperature in the dark. After adding 50 μL of stop solution, the optical density at 450 nm of each well was determined. The MMP-2 and MMP-9 concentrations for each sample were calculated from the standard curve. The MMP-2 assay recognized both pro- and active-forms of MMP-2. Intra-assay and inter-assay coefficients of variation (CV) were 4.8% and 7.7%, respectively. Minimum detectable dose (MDD) of MMP-2 assay was 0.16 ng/mL. The MMP-9 assay recognized both pro- and active- forms of MMP-9. The intra-assay and inter-assay CV were 2.3% and 7.5%, respectively. The MDD was less than 0.156 ng/mL. According to the manufacturer's brochure, no significant cross-reactivity or interference to various proteins, including mutual cross-reactivity between MMP-2 and MMP-9, was observed.

Statistical Analysis

Data analysis started with descriptive statistics, including mean and standard deviation for continuous variables, and frequency for categorical variables. The Mann-Whitney test was applied for comparing the MMP-2 and MMP-9 levels and activities between patients and control subjects. An alpha level of 0.05 was used for all statistical tests.

Results and Discussion

A high proportion of diabetic patients of long duration develop various diabetic complications. The most devastating diabetic complications are those that affect blood vessels and the most important microvascular diabetic complications are diabetic nephropathy and retinopathy. Diabetic nephropathy is the single most common disorder leading to renal failure. Thus, a better understating of diabetic pathogenesis and nephropathy pathophysiology could lead to the design and development of urgently needed new treatment approaches.

MMPs are one of the numerous factors that have been implicated in diabetic nephropathy. Although the MMP induction/expression system, including MMPs and tissue inhibitors of matrix metalloproteinase (TIMPs), is implicated in diabetic complications, experimental data suggest that localized renal MMP-2 and MMP-9 are the major MMPs that take part in the pathogenesis of diabetic nephropathy (4–6). Nevertheless, results regarding MMP-2 and MMP-9 levels and activities in diabetic complications remain controversial.

MMP-2 and MMP-9 activities in sera from our study subjects were analyzed by zymography. Representative results of the zymographic data are shown in Fig. 1. The data showed that both MMP-2 and MMP-9 activities in sera from patients with T1DM were significantly higher than those from control subjects. When the MMP-2 and MMP-9 expression levels were quantitatively measured by ELISA, the MMP-2 level in control subjects and T1DM patients was 146.1 ± 34.2 and 241.5 ± 73.7 ng/mL, respectively (Table 2). The MMP-9 level in control subjects and T1DM patients was 51.4 ± 57.1 and 305.3 ± 180.6 ng/mL, respectively (Table 2). Both MMP-2 and MMP-9 levels were significantly higher in sera from all patients, compared to those from control subjects. No significant correlation between MMP levels or activities with patients' demographic or clinical data was found.

The major observations of our study are that MMP-2 and MMP-9 levels and activities are higher in T1DM patients compared to those of control individuals. In addition to ELISA, our study also measured MMP activities by zymography, which can provide information complementary to the results of direct enzyme assay by solution methods. Both ELISA and zymography results confirmed that MMP levels and activities were elevated in diabetic patients. In addition, we had recruited 201 T1DM patients from the Taiwanese population, with one of the lowest diabetic incidences worldwide (1), as well as a relatively large pool of control subjects. Therefore, our data should be sufficient to faithfully reflect and represent the MMP alterations in Taiwanese diabetic patients.

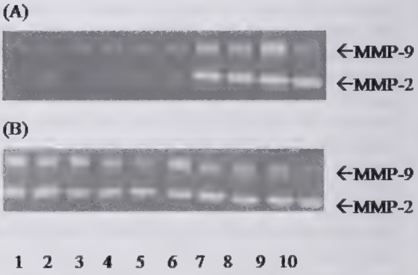

Figure. Representative SDS-PAGE zymogram showing that MMP-2 and MMP-9 activities were elevated in patients with T1DM. MMP-2 and MMP-9 activities in sera from study subjects corresponds to the upper and lower white lytic bands, respectively. (A) Lanes 1~6, healthy control individuals; lanes 7~10, T1DM subjects; (B) T1DM subjects.

TABLE 2
Levels of MMP-2 and MMP-9 in Control Subjects and Type 1 Diabetes Mellitus Patients

	Study Subjects	
	Control (n=189)	**T1DM (n=201)**
MMP-2 (ng/mL)*	146.1±34.2	241.5±73.7**
MMP-9 (ng/mL)*	51.4±57.1	305.3±180.6**

*Data are presented as mean ± standard deviation.
**$p<0.05$ by Mann-Whitney test, compared with the levels of control subjects.
MMP = metalloproteinase.

Our results support earlier observations that both MMP-2 and MMP-9 levels in diabetic subjects are higher than in nondiabetic subjects (16). Nevertheless, contradictory results exist. Though Maxwell et al. reported significantly increased concentrations of plasma MMP-9, they found no significant difference in plasma MMP-2 between diabetic patients and controls (13). On the other hand, Derosa et al. found that MMP-2 levels and activities were significantly higher in type 1 diabetic patients and T1DM patients with complications than in nondiabetic subjects (14). No significant differences were observed for MMP-9 level and activity in that study.

Several factors, such as methodological variations and statistical power, may contribute to the discrepancies of the results between the above studies and our observations. The MMP assay systems used in Maxwell's study can only recognize free and complexed MMPs; they cannot provide information on the active MMP forms (13). Therefore, the increased plasma MMP-9 and TIMP-1 levels in their study reflect increased synthesis. Their study population is perhaps too small (43 patients and 35 control individuals were recruited) to investigate the relationship between MMPs and diabetic duration or metabolic control. Because the T1DM patients recruited in that study had normal renal function without microalbuminuria, the authors suggest that diabetic environment can alter gene expression of both MMPs and TIMP-1 prior to the onset of clinically apparent complications.

Derosa et al. (14) used 2 ELISA kits to differentiate MMP levels and activity. The authors concluded that the observation of significant difference in MMP-2 levels and activity, in contrast to MMP-9 levels and activity between T1DM and control subjects, might be due to the youth and the good metabolic control of their patients. The study was designed to longitudinally and retrospectively detect the MMP levels and activity at T1DM onset and 5-year follow-up in a fixed population. Therefore, compared to the study of Maxwell et al. (13), Derosa's study should be able to more faithfully reflect the temporal alteration of MMP levels and activity during disease progression in diabetic patients. Nevertheless, the number of Derosa's study subjects is even smaller: only 25 T1DM patients, and only 15 of the 25 developed microangiopathy during follow-up. Therefore, whether the investigative power of their study is sufficient to truly represent the relationship between MMPs and diabetes needs further clarification.

There are several limitations to our study. First of all, the age of our diabetic patients and control subjects (mean age 14.4 ± 0.6 and 58.2 ± 10.6 years old respectively, Table 1) was not matched. Neither Maxwell (13) nor Derosa (14) found a correlation between MMP-2, MMP-9 and age. Derosa et al. indicated that though both MMP-2 and MMP-9 levels were slightly increased in all study subjects at 5-year follow-up compared with that of their baseline levels, the increasing trend has no statistical significance. Accordingly, MMP levels of our older control group should have been higher than that of the younger diabetic subjects. The age mismatch between the T1DM and control subjects might not affect the validity of our data, since our results demonstrated significantly higher MMP levels in the much younger T1DM patients.

Secondly, pro-MMPs are actually inactive in serum, but would be activated during the zymography renaturing step and become fully active in the gels. Kleiner et al. (15) indicated that zymography is an extremely sensitive electrophoretic technique that has been extensively used in the qualitative evaluation of both active and latent forms of gelatinases present in tumors. The electrophoretic process can efficiently separate these enzymes from endogenous inhibitors, and both active and latent forms of MMPs would show the same degree of digestion in the assay. Only pro forms of MMPs can be detected in zymography gel when MMP levels are low (~≤ 200 pg). The active form cannot be detected until the MMP levels are higher than approximately 400 pg. When the MMP levels are high, latent and active forms of these enzymes are present in approximately a 7:1 ratio. The authors also concluded that it is not biochemically unreasonable, using zymography, to determine enzyme activity and hence total enzyme protein. Thus, the assay can be used to quantitate not only total enzyme, but also the proportion of enzyme present in both the latent and active forms. This ability distinguishes zymography from whole solution methods such as ELISA, which quantitate total enzyme but do not distinguish between different molecular weight forms, and from solution activity assays, which can only quantify the active forms of the enzymes (15). Accordingly, it is suggested that the zymography results may reveal the MMP activities in study subjects because of the much higher MMP levels in our study subjects than the detection limit, and the relatively stable proportion of pro- and active-MMPs in circulation.

Thirdly, the anticoagulant EDTA used in blood collection may affect the MMP levels and activities in our study. Jung et al. (17) demonstrated that MMP-9 concentration is decreased significantly with increasing amounts of EDTA during blood collection, whereas MMP-2 is increased. They also revealed that EDTA can inhibit the gelatinolytic activities. Mannello et al. (18) indicated that MMP-2 level did not differ in serum and heparin plasma but was lower in EDTA plasma, while activities of MMP-9 were 2- to 10- fold higher in serum than in heparin and EDTA plasma. Nevertheless, different anticoagulants used in blood sample collection did not influence the proportion of active-to-latent MMPs. Although the anticoagulant of this study was EDTA, which is reported to affect circulatory MMP levels or activities, we do not think that EDTA affected the observation regarding the significantly increased MMP-2 and MMP-9 of T1DM patients in our study, since EDTA was applied to the blood collection process of all study subjects. Therefore, if EDTA did cause alterations to circulatory MMP levels and activities, this variable became a controlled factor in our study.

And finally, the average duration of our T1DM patients in this study was 4.5 ± 0.2 years (Table 1); only 15 patients (7.5%) suffered T1DM for more than 10 years. Most of the patients had no symptoms of diabetic nephropathy or other complications. Therefore, the number of patients with complications in our study was not sufficient to reflect and represent the correlation between MMPs and diabetic complications, due to limited investigation power from an insufficient number of patients with complications. The results of our study suggest that the MMP levels would be elevated before the development of diabetic nephropathy or other complications (4).

In summary, our study not only provides data on systemic MMP levels in a population with possibly the lowest type 1 diabetic incidence, but also suggests that MMP expression and activity is elevated before the onset of complications in diabetic patients, due to the relatively short duration and lack of complications among our study subjects. Whether there is a correlation or interactions between autoimmune responses and MMP system awaits further investigation, as does the role of MMPs in the T1DM pathogenesis.

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Tuberculous Meningitis Presenting with Unusually Severe Hyponatremia

Bernardino Roca, M.D., Ph.D., and Daniel Bahamonde, M.D.

Abstract

We report a patient with tuberculous meningitis who presented with unusually severe hyponatremia, an electrolyte disorder that may cause symptoms similar to those of tuberculous meningitis. The hyponatremia was probably due to the syndrome of inappropriate antidiuretic hormone secretion, and resolved after instituting water restriction and antituberculous medication.

Key Words: Meningitis, hyponatremia, tuberculosis.

Introduction

TUBERCULOSIS involves the central nervous system (CNS) in approximately 10% of patients, with tuberculous meningitis (TM) as the most common presentation (1). TM may present acutely, with altered sensorium, neck rigidity and fever, or much more subtly, with malaise, headache and minimal mental changes. Therefore, for many patients the diagnosis is not easy, and a high index of suspicion is necessary to recognize it. Unfortunately, when TM is not diagnosed and treated early, mortality and permanent disability rates are high (2).

We describe a case of TM that presented with only subtle signs of meningitis, and lethargy induced by severe hyponatremia, which made the correct diagnosis particularly difficult.

Case Report

A 28-year-old male presented with a 10-day history of headache, malaise and low-grade fever, which had not responded to amoxicillin/clavulanate. On the day of admission, he also had a generalized seizure. His medical record included appendectomy, and tobacco and alcohol abuse. Born in Romania, he had arrived in Spain two weeks before admission. All his relatives were in good health. After recovering from the seizure, he was obtunded, but without focal neurologic deficits; temperature was 37.6°C and breath sounds were diminished in the left thorax base; otherwise, physical examination was normal.

Blood laboratory tests revealed severe hyponatremia and decreased osmolality (Table); potassium level was 4.3 mEq/L, creatinine 0.9 mg/dL, blood urea nitrogen 18.2 mg/dL, and uric acid 3.2 mg/dL. All other blood results, including hematology values, chemistries, blood pH and gas analysis, cortisol, thyroid hormones and coagulation tests, were normal. Urine analysis showed inappropriately high osmolality (Table); all other results were normal. Lumbar puncture, carried out on the day of admission, disclosed a mildly turbid cerebrospinal fluid (CSF), with glucose 16 mg/dL (normal: 40 – 70 mg/dL), protein 111 mg/dL (normal: 15 – 50 mg/dL), white blood cells 90 per mm^3 (60% neutrophils and 40% lymphocytes) (normal: < 5 mononuclear cells per mm^3), and adenosine deaminase 16 IU/L (normal: < 8 IU/L). Chest radiographs revealed a minimal left pleural effusion. The specimen obtained by ultrasound-guided diagnostic thoracentesis was inadequate for laboratory tests. Initially, all microbiologic studies, including those of blood, urine, CSF, sputum and pleural effusion, were negative. An electrocardiogram was normal. Computed tomography (CT) scan and magnetic resonance imaging (MRI) of the head revealed minimal hydrocephalus affecting both lateral ventricles. CT scans of the chest and abdomen were normal except for a small left pleural effusion.

When we received CSF analysis results, we instituted treatment with dietary water restriction, saline perfusion, isoniazid, rifampin, pyrazinamide, ethambutol, ceftriaxone, vancomycin, ampicillin, phenytoin, and dexamethasone. The patient's condition slowly improved over the next hours and days, and by the end of the first week of therapy he was completely asymptomatic. In the second week of therapy *Mycobacterium tuberculosis* grew in the CSF, and treatment was continued with isoniazid, rifampin, pyrazinamide, and ethambutol. The organism was susceptible to all first line antituberculous medications. A repeated CT scan of the head was normal.

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TABLE
Sodium Concentration and Osmolality Results in Blood and Urine.

Days after Admission	0	3	6	9
Blood sodium (mEq/L)	113	116	120	136
Blood osmolality (mOsm/kg)	230	241	NA	NA
Urine sodium (mEq/L)	29	33	NA	NA
Urine osmolality (mOsm/kg)	533	527	NA	NA

NA = not available.

Discussion

TM usually results from the hematogenous spread of primary or postprimary pulmonary infection or from the rupture of a subependymal tubercle into the subarachnoid space. Hydrocephalus and paresis of cranial nerves occur frequently in patients with TM. Other neurologic complications, such as brain edema, focal ischemia, myelitis, arachnoiditis, empyema, syringomyelia, etc. are less common, but they must be kept in mind in order to establish an early diagnosis and treatment (3).

Hyponatremia can result from many disease states, injury, surgery, physical exercise, advanced age, or the administration of certain drugs, such as diuretics, antidepressants or anticonvulsants (4). Clinical manifestations of hyponatremia are related to increased intracellular fluid volume, specifically brain cell swelling or cerebral edema, due to osmotic water shift. For this reason, symptoms are mainly neurologic, and their severity depends on the rapidity of onset and absolute decrease in plasma sodium concentration. Patients with mild hyponatremia may be completely asymptomatic or they may complain of nausea, malaise, dizziness, and headache. As sodium concentration falls, symptoms may progress to include lethargy, confusion, obtundation, and psychosis. If concentration falls below 120 mEq/L or diminishes rapidly, stupor, seizures, and coma are also possible. Even death may occur, although it is more commonly due to the underlying disorder than to hyponatremia itself (4).

Clinical presentation of hyponatremia and TM are partly similar; therefore, there is the risk that TM diagnosis will be overlooked when both conditions coexist, which may have deleterious consequences for patients. Symptoms in our patient were initially thought to be due to hyponatremia, with improvement in obtundation and most other symptoms after institution of treatment for hyponatremia. Nevertheless, the presence of fever and hydrocephalus, as well as the initial absence of an explanation for hyponatremia, led us to perform a lumbar puncture, which enabled us to establish the diagnosis of TM.

For patients who present with extracellular fluid volume contraction or expansion, the etiology of hyponatremia is obvious in most cases. Measuring serum osmolality, urine sodium concentration and urine osmolality may also help to differentiate among the possible causes of the electrolyte disorder (5). The syndrome of inappropriate antidiuretic hormone secretion (SIADH) as a cause of hyponatremia is a diagnosis of exclusion, requiring a thorough search for all other possible etiologies (5). SIADH, a classic presentation of TM, as well as other forms of tuberculosis (6, 7), was probably the cause of hyponatremia in our patient. Most of the other etiologies of the electrolyte disorder could be easily ruled out (5). Moreover, the response of hyponatremia to water restriction and saline perfusion, and the lack of recurrence after initiating antituberculous treatment also favor SIADH, induced by TM, as the cause of the electrolyte disorder (8).

Urine sodium in our case was lower than expected, probably reflecting low solute intake. It is generally recommended that correction of hyponatremia be faster than it was in our case (9), although rapid correction of the electrolyte disorder has been related to pontine and extrapontine myelinolysis (10). High-dose steroid treatment may have contributed to the slow decline in sodium level in our patient (4, 5).

In brief, this case is a classic example of TM presenting with hyponatremia, although the electrolyte disorder was unusually severe.

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Orbital Dystopia Managed with Unilateral Brow Suspension

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Abstract

Patients with orbital dystopia present with symptoms of diplopia and/or facial asymmetry. Repositioning of the orbit requires multiple osteotomies around the orbit, which presents significant complications. The authors present an alternative method to restore facial symmetry in the case of a 14-year-old patient with congenital orbital dystopia due to fibrosis of the sternocleidomastoid muscle. The patient had no ocular symptoms but did have asymmetric descent of the ipsilateral brow. He refused box osteotomy and repositioning of the orbit. Unilateral brow suspension was performed using an endoscopic technique and suspension sutures fixed to resorbable screws. Adequate brow elevation was noted in the immediate postoperative period and at 6 months; it successfully restored facial symmetry.

Key Words: Orbit, dystopia, endoscopic, brow.

Case Report

A 14-YEAR-OLD MALE presented with orbital dystopia and periocular asymmetry. Parturition required forceps secondary to a transverse presentation. According to the patient's mother, the use of forceps resulted in a hematoma around the left side of the face and neck. Resolution of the hematoma yielded fibrosis and shortening of the ipsilateral sternocleidomastoid muscle. This was treated with early physical therapy, which was unsuccessful in preventing ultimate asymmetric growth of the facial skeleton.

Through childhood, the patient was followed to see if he was improving, but no surgical intervention was undertaken. He presented again as a teenager with concerns about the asymmetric appearance of his face. Notably, he had several millimeters of brow ptosis on the left as compared to the right (Fig. 1). There was also 1–2 millimeters of enophthalmos. However, the patient reported no problems with vision, including diplopia, and did not wear eyeglasses. On examination, he had full extraocular muscle excursion. His pupils were equal in size and shape and reactive to light. The nasal pyramid was midline and his occlusion was Angle class I.

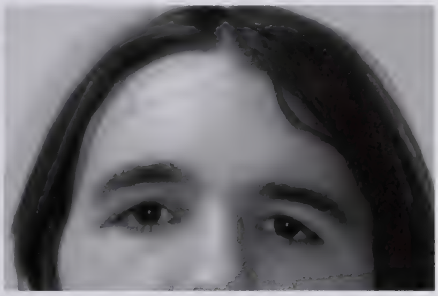

Fig. 1. Preoperative photograph of a 14-year-old male with orbital dystopia and malposition of the left brow.

A CT scan of the head was performed at 1.25 mm intervals and reconstructed as a three-dimensional image (Fig. 2). There was obvious asymmetry of the orbital shape and position. On the unaffected right side, the superior limit of the orbit extended higher than that on the left. This caused the soft tissue envelope of the left periorbita to remain

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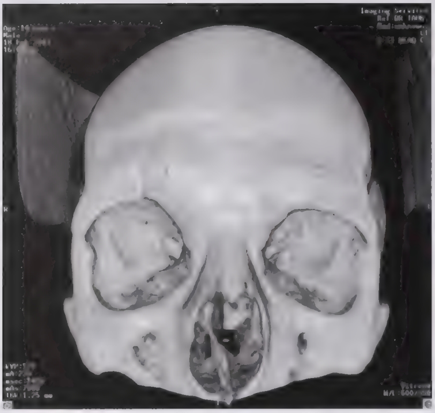

Fig. 2. Preoperative 3-dimensional CT scan of the head.

suspended at a more inferior position than the contralateral side.

Informed of the procedure for realigning the orbits, the patient and his family chose unilateral brow elevation as a means of correcting the resultant ptosis and camouflaging the dystopia. He underwent a unilateral left endoscopic unilateral brow elevation. The periorbita around the left orbit was detached from the orbital rim and the soft tissues of the eyebrow were re-suspended with Prolene sutures in the dermis. Resorbable screws in the skull (KLS, Jacksonville, FL), posterior to the hairline, were used to anchor the sutures. At 6 months (Fig. 3) the patient had improved symmetry of the face, as evidenced by a more symmetric appearance of the palpebral fissures and eyebrow position to the contralateral side.

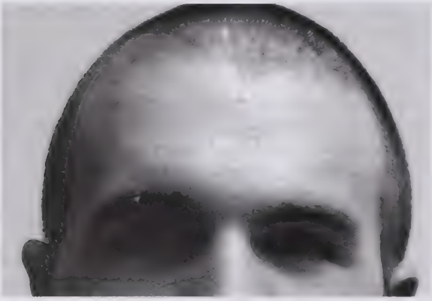

Fig. 3. Six-month postoperative photograph showing improved periorbital symmetry following left unilateral endoscopic browlift.

Discussion

Orbital dystopia is defined as an asymmetry in either the vertical or horizontal position of one or both hemi-orbits in at least one of the three-dimensional planes (1). As a result of the bony asymmetry, the soft tissues attached to the orbital margins mirror the underlying malposition. The condition may or may not be associated with visual problems, such as diplopia.

Treatment of orbital dystopia is arguably best addressed by reconstructing the underlying bony framework (2, 3). Multiple incisions (bicoronal, lower eyelid, gingivobuccal sulcus) and several osteotomies are required to mobilize and reposition the orbital rim to match the unaffected side. Hospital admission is required for postoperative monitoring of potential neurologic and ophthalmologic complications, which are not insignificant. Finally, the overall cost of treatment can be burdensome.

Endoscopic (or open) browlift, by contrast, is a less invasive and relatively straightforward procedure. This approach is presented here as an alternate means of addressing the facial asymmetry associated with orbital dystopia. While not addressing the underlying problem, the technique does offer improved symmetry with relative ease and minimal potential for complication. It may be performed on an outpatient basis and thus at a lower cost. Unlike the situation with orbital repositioning, the risk for intracranial and globe injury is relatively nonexistent.

The main disadvantages of brow lifting include the potential for residual asymmetry in brow position and for relapse in the later postoperative period. In the case described, the position of the eyebrow was set a couple of millimeters higher to allow for descent of the eyebrow in the immediate postoperative period, as occurred with healing and resolution of edema. Furthermore, it has yet to be determined whether the long-term results equal those in the early postoperative period. The procedure, however, does not preclude later orbital repositioning if less invasive procedures, such as the one described here, fail to adequately correct the problem over time.

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Pregnancy in the Patient with Eisenmenger's Syndrome

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Abstract

Eisenmenger's syndrome occurs when a large congenital or surgically created shunt between the left and right sides of the heart causes an increase in pulmonary vascular resistance that equals or surpasses systemic resistance, resulting in a reversal of the shunt from a left-to-right shunt to a right-to-left or bi-directional shunt. The maternal mortality rate of pregnancy in the presence of Eisenmenger's syndrome is reported to be as high as 50–65% with cesarean section. We present the case of a 32-year-old woman with Eisenmenger's syndrome who gave birth at 29 weeks of gestation via C-section to a healthy baby boy, and we review the literature regarding the management of such patients.

Key Words: Eisenmenger's syndrome, pregnancy, congenital heart disease.

Introduction

IN PATIENTS with a congenital left-to-right shunt, a progressive increase in pulmonary vascular resistance may lead to shunt reversal or bi-directional shunting, resulting in Eisenmenger's syndrome. It occurs in these patients secondary to irreversible damage to the pulmonary vasculature from prolonged exposure to systemic pressures due to the left-to-right shunting. When right-sided pressures meet or exceed systemic pressures, a reversal occurs in the shunt, leading to the morbidity and mortality associated with this condition. These hemodynamic changes may lead to thromboembolic events, cerebrovascular complications, or the hyperviscosity syndrome. Pregnancy or noncardiac surgery is associated with a high mortality rate in patients with this syndrome. Most patients with the syndrome survive for only 20–30 years (1–4).

The increased pulmonary resistance that occurs in Eisenmenger's syndrome carries a serious prognosis during pregnancy. During the antepartum period, the decreased systemic vascular resistance associated with pregnancy increases the likelihood and the degree of right-to-left shunting, and therefore cyanosis to both the mother and the fetus may ensue. The maternal mortality rate of pregnancy in the presence of Eisenmenger's syndrome is reported to be as high as 50–65% with cesarean section. Overall fetal wastage is reported to be up to 75%. Medical termination of pregnancy is the preferred management for women with Eisenmenger's syndrome who present early in pregnancy (5, 6). We present the case of a 32-year-old woman with Eisenmenger's syndrome who gave birth at 29 weeks of gestation to a healthy baby boy, and we review the literature regarding the management of such patients.

Case Summary

A 32-year-old African American woman with a history of congenital cyanotic heart disease with tricuspid atresia, transposition of the great vessels, irreversible pulmonary hypertension, double outlet left ventricle, patent ductus arteriosus (PDA), and patent foramen ovale (PFO) presented to our cardiology clinic during her third month of pregnancy. She had never undergone surgery to correct her cardiac defects. This was the patient's first pregnancy, and she was referred to our clinic from her pediatric cardiologist.

The patient related progressive cyanosis and dyspnea on exertion over the prior several years. Her medical regimen included digoxin and

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furosemide daily. On physical examination, the patient's blood pressure was 145/85 mm Hg, her pulse was 80/min, and oxygen saturation was 80–88%. Her lungs were clear to auscultation, and cardiac exam showed regular rate and rhythm with a preserved S1 and S2, but revealed a palpable thrill over the right sternal border and a III/VI continuous murmur at the right upper sternal border and the mid-scapular area. A ventricular heave with a bounding apical impulse was also noted. No peripheral edema was observed. Her ECG revealed sinus rhythm at a rate of 80 beats/min with significant voltage, indicating ventricular hypertrophy.

Five years earlier, the patient had undergone cardiac catheterization (Figure). At that time her right atrial (RA) pressure was 16–18 mm Hg, and her pulmonary artery (PA) pressure was 106/46 mm Hg. Pulmonary capillary wedge pressure (PCWP) was 20 mm Hg and the left atrial (LA) pressure was 16–24 mm Hg. Left ventricular (LV) pressure was 106/14 mm Hg, and the ascending aorta pressure was 106/66 mm Hg. The shunt ratio (Qp:Qs) was 2.2:1. Echocardiography showed a dilated double-outlet left ventricle with unrestricted pulmonary blood flow and an ejection fraction of 33%. Severe pulmonary hypertension and tricuspid atresia were also noted.

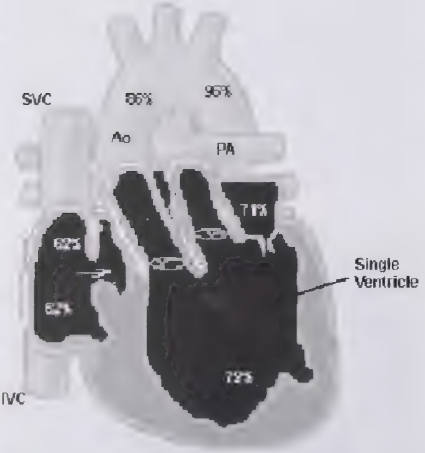

Figure. Diagram detailing this patient's congenital anomaly. The percentages on the diagram are the oxygen saturations noted in these cardiac chambers at catheterization. The arrow reveals the defect in the atrial septum. (SVC=superior vena cava; IVC=inferior vena cava, Ao=aorta; PA=pulmonary artery; PDA=patent ductus arteriosus).

The patient had been told several times that she should undergo termination of her pregnancy, given the serious danger imposed on her and the fetus by her congenital anomaly. This recommendation was reiterated during our first encounter with her. However, she chose to continue her pregnancy.

Over the next few months, the patient underwent frequent close follow-up with both the cardiology clinic and the high-risk obstetrics clinic. At 27 weeks, she was admitted to the hospital in anticipation of labor induction and monitored on telemetry. Fetal monitoring was also undertaken. The patient was maintained on bed rest, supplemental oxygen, and heparin. Transthoracic echocardiography revealed pulmonary artery pressure of 95 mm Hg and a Qp:Qs ratio of 2:1. The issue of the optimal time of elective C-section to optimize fetal development while hoping to minimize maternal risk was considered. At 29 weeks, labor ensued and delivery of the baby via C-section was undertaken. At that time, the patient also had fallopian tubal ligation. Both she and the baby did well in the postpartum period. The patient was monitored after the C-section, and then discharged to home. She continues to follow up with us in cardiology clinic. She is maintained on home oxygen, digoxin, furosemide, and warfarin anticoagulation; and she continues to do well.

Discussion

Congenital defects associated with Eisenmenger's syndrome include ventricular septal defect (VSD), atrial septal defect (ASD), atrioventricular defects, PDA, D-transposition of the great vessels, and surgically created aortopulmonary connections. Since the first description by Vicktor Eisenmenger in 1897 (7), it has been noted that about 8% of all patients with congenital heart disease and about 11% of those with left-to-right cardiac shunting develop the Eisenmenger syndrome (1, 8). Approximately 50% of infants with a large, nonrestrictive VSD or PDA develop increased pulmonary resistance by early childhood, and 40% of patients with a VSD or PDA and transposition of the great arteries develop pulmonary hypertension within the first year of life. With a large secundum ASD, only 10% of cases progress to pulmonary hypertension, and they do so more slowly and usually not until after the third decade of life. In almost all patients with persistent truncus arteriosus and unrestricted pulmonary blood flow, and almost all patients with common atrioventricular canal, severe pulmonary resistance develops by the second year of life. With surgically created systemic-to-pulmonary shunts, the frequency of pulmonary hypertension varies depending on size and anatomy of the shunt (1, 2, 8–10).

Patients who develop Eisenmenger's syndrome generally present with impaired exercise tolerance due to an inability to increase pulmonary blood flow. This inability to increase pulmonary blood flow, limits oxygen uptake. Other symptoms include subtle neurologic abnormalities such as headache, dizziness, or visual disturbances due to erythrocytosis and hyperviscosity. In addition, arrhythmias are common, and may lead to sudden death. Hemoptysis may also occur, due to damage of the pulmonary vasculature. Cerebrovascular accidents may occur as a result of paradoxical embolization, venous thrombosis of cerebral vessels, or intracranial hemorrhage. In addition, patients may also develop a brain abscess (10).

The pathophysiology of Eisenmenger's syndrome consists of the initial morphologic alterations (medial hypertrophy of the pulmonary arterioles, intimal proliferation and fibrosis, and occlusion of the small vessels), which are potentially reversible. As the disease progresses, more advanced morphologic changes (plexiform lesions and necrotizing arteritis) are irreversible. The result is obliteration of much of the pulmonary vascular bed, leading to increased pulmonary vascular resistance and reversal of the shunt (11).

Whatever the etiology of Eisenmenger's syndrome, increased pulmonary resistance carries a grave prognosis during pregnancy. During the antepartum period, the decreased systemic vascular resistance associated with pregnancy increases the likelihood and the degree of right-to-left shunting. The increase in right-to-left shunting decreases pulmonary perfusion. This decrease results in hypoxemia to both the mother and the fetus. In such a patient, systemic hypotension leads to a decreased right ventricular filling pressure, and in the presence of fixed pulmonary resistance, such decreased right heart pressure may be insufficient to perfuse the pulmonary arterial bed. This insufficiency may result in sudden profound hypoxemia and death. Maternal hypotension during pregnancy can result from hemorrhage or complications of anesthesia. This sequence of events is the principal clinical concern in the peripartum management of patients with increased pulmonary resistance (11–13).

The rate of survival among patients with Eisenmenger's syndrome is 80% ten years after diagnosis, 77% at 15 years, and 42% at 25 years (14, 15). Death usually occurs suddenly, presumably caused by arrhythmias, but some patients die of heart failure, hemoptysis, a brain abscess, or a stroke. A history of syncope, right ventricular systolic dysfunction, low cardiac output, and severe hypoxemia indicates a poor prognosis (1, 8).

The treatment of patients with Eisenmenger's syndrome is difficult. Intravascular volume depletion, heavy exertion, high altitude, and the use of vasodilators should be avoided. Because of high maternal and fetal morbidity and mortality, pregnancy should also be avoided. Although no therapy has been proven to reduce pulmonary vascular resistance, intravenous epoprostenol may be beneficial (16). Phlebotomy with isovolumic replacement should be performed in patients with symptoms of hyperviscosity (17). For patients who have markers of poor prognosis such as syncope, right heart failure and/or severe hypoxemia, lung transplantation with repair of the cardiac defect or combined heart-lung transplantation is an option (18). Because of the reasonably good likelihood of survival among patients treated medically and the limited success of transplantation, the latter should only be used as a last resort in carefully selected patients.

Eisenmenger's syndrome is an absolute contraindication to pregnancy and if a patient with this syndrome does become pregnant, early termination is highly recommended due to the maternal mortality (as high as 50%). Yentis et al. (19) examined the maternal mortality in a group of patents from 1990–1995 and found that, similar to initial reports from the 1950s, maternal mortality remains high—around 40%—and fetal loss about 8%. Only 15% of infants studied were born at term. Maternal mortality associated with Eisenmenger's syndrome therefore remains as high as it has been for the past 50 years (19).

Researchers have looked at methods to decrease maternal mortality in pregnancy with Eisenmenger's syndrome. Avila et al. (20) examined a group of 13 pregnancies among 12 patients. They found three spontaneous abortions, one premature labor at 23 weeks of gestation and two maternal deaths during the 23rd and 27th weeks of gestation. Seven of the 12 patients reached the end of the second trimester. This group was hospitalized until delivery and received heparin (20,000–40,000 units per day) and oxygen therapy. Cesarean section was performed on all patients as a result of worsening maternal or fetal clinical condition during the third trimester of gestation. All of the mothers were discharged from the hospital, but one of them died on the 30th post-partum day. These investigators concluded that although pregnancy should be discouraged in women with Eisenmenger's syndrome, it can be successful with prolonged bed rest and the use of heparin and oxygen therapy to improve maternal and infant outcomes (20). Other studies, however, have found a negative effect of heparin prophylaxis in these patients (21). Thus the role of anticoagulation in the care of pregnant patients with Eisenmenger's syndrome remains controversial.

Inhaled nitric oxide is a potent and selective pulmonary vasodilator used in patients with pulmonary hypertension. It is thought that direct inhalation of nitric oxide may reduce pulmonary resistance and improve oxygenation because of optimization of ventilation-perfusion relations. There have been reports of nitric oxide use during pregnancy in patients with Eisenmenger's syndrome (22). Goodwin et al. (23) report the case of a 27-year-old woman treated with nitric oxide to correct the refractory hypoxemia of Eisenmenger's syndrome during the birth of her 36-week-old infant. Despite continued vasodilator therapy, however, the patient died on post-partum day 6. Another report by Lust et al. (24) cites the use of nitric oxide in the peripartum period of a 29-year-old primigravid female at 34 weeks' gestation. After giving birth, however, she died of worsening pulmonary hypertension and heart failure on post-partum day 21 (24).

Conclusion

Patients with Eisenmenger's syndrome should be counseled against becoming pregnant. Eisenmenger's syndrome is an absolute contraindication to pregnancy, and if a patient with this syndrome does become pregnant, early termination is highly recommended due to high maternal mortality. Maternal mortality associated with Eisenmenger's syndrome, despite recent efforts at its mitigation, remains as prevalent as it has been for the past 50 years. We presented the case of a 32-year-old woman with Eisenmenger's syndrome who, despite medical advice, decided to continue her pregnancy and gave birth to a healthy baby at 29 weeks' gestation.

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HIV-Related Pulmonary Hypertension

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Abstract

With the availability of better treatment and prophylactic regimens for the infectious complications of human immunodeficiency virus (HIV), the non-infectious complications are gaining greater attention. HIV-related pulmonary arterial hypertension (HIV-PAH) is one of these. The incidence of HIV-PAH is estimated at 0.5% of HIV-infected individuals. The pathogenesis remains unclear. Patients present with symptoms as diverse as progressive shortness of breath, pedal edema, dry cough, fatigue, syncope, as well as chest pain. Chest X-ray always shows cardiomegaly and prominent pulmonary artery, and evidence of right ventricular hypertrophy can be seen from the electrocardiogram. The pulmonary arterial systolic pressure, diastolic pressure and pulmonary vascular resistance from right heart catheterization are increased.

There are a few small studies showing the benefit of prostacyclin analog (epoprostenol and iloprost) and bosentan. The role of antiretrovirals remains controversial, as do those of other agents such as calcium channel blockers and anticoagulants. The prognosis of HIV-PAH is grave. Two thirds of HIV-PAH related mortality is usually secondary to consequences of pulmonary hypertension, with the worst survival noted in New York Heart Association (NYHA) functional class III-IV. The probability of survival in one series was 73%, 60% and 47% at one, two and three years, respectively.

Key Words: HIV-related pulmonary hypertension, AIDS-related pulmonary disease, pulmonary hypertension, epoprostenol, highly active antiretroviral therapy.

Introduction

HUMAN IMMUNODEFICIENCY VIRUS INFECTION has been associated with both infectious and non-infectious complications. With the advent of better prophylaxis against opportunistic infections, as well as longer survival secondary to new and potent antiretroviral treatments, non-infectious complications of HIV are gaining greater recognition and attention.

Many cardiovascular complications of HIV infection are well known and have been well described. These include cardiomyopathy, pericarditis and/or pericardial effusion, as well as myocarditis. Pulmonary hypertension (PH) has recently also been recognized as one of the outcomes of HIV infection and is now known to be one of the most devastating non-infectious complications.

Kim and Factor (1) reported the first known case of PH in a non-hemophiliac, homosexual HIV-positive subject in 1987. Since the publication of their case report, an increasing number of HIV-PAH patients have been identified. To date, more than 200 cases have been reported (2–26).

In this article, we present a comprehensive review of the epidemiology, pathogenesis, pathology, clinical features, and natural course of HIV-related pulmonary hypertension. In addition, available treatments are critically evaluated and discussed in association with the outcome and prognosis of HIV-PAH. Where relevant, recently published clinical and experimental evidence is examined and presented concisely for a comprehensive review of the topic.

Epidemiology

The prevalence of HIV-PAH has been estimated at 1:1,200 (0.5 %) of HIV-infected individuals, 8.1% of whom have cardiopulmonary complaints, as compared to 1–2:1,000,000 patients of idiopathic pulmonary hypertension (IPAH) in the

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general population (2). However, it is estimated that the true prevalence of HIV-PAH is much higher, since most published studies evaluating HIV-PAH are unable to include the asymptomatic cases.

A 1992 report indicated that HIV-infected individuals had severe but significantly lower levels of PH than was common among those with non-HIV primary pulmonary hypertension (3), a phenomenon that is attributed to closer medical attention, leading to earlier diagnosis in the first group. The mean age at the time of diagnosis of HIV-PAH cases was 32, with a male-to-female ratio of 1.6:1 versus with 1:1.7 in IPAH (4).

A 1998 review by Mesa et al. (4) identified the following risk factors for HIV infection: intravenous drug abuse (IVDA) 42%, homosexuality 25%, hemophilia 13%, heterosexual transmission 10%, blood transfusions for non-hemophiliacs 4%, both homosexual and IVDA 3%, and maternally acquired congenital infection 4%. In the year 2000, Mehta et al. (5) reviewed 131 cases of HIV-PAH and found that among 82% of infected individuals, PH was related solely to HIV infection without other secondary causes.

HIV-PAH has been shown to occur in both the early and later stages of HIV infection and does not seem to be related to the degree of immunodeficiency or the CD4+ T-lymphocyte counts. However, the severity of HIV-PAH (determined by pulmonary arterial systolic pressure [PASP]) was higher in patients with full-blown AIDS than in non-AIDS HIV-infected patients (27).

Pathogenesis

The pathogenesis and exact mechanism of development of pulmonary hypertension in patients with HIV have not been clearly defined. Pathologically, HIV-PAH is characterized by significant remodeling of the pulmonary vasculatures.

In 1988, Goldsmith et al. (6) presented a case report of five HIV patients with hemophilia A that had been treated with self-administered lyophilized concentrates of Factor VIII; all of these patients developed pulmonary hypertension without other identifiable underlying cardiac or pulmonary disease. The authors concluded that the interval development of PH in this particular group of patients may have been related to the treatment with lyophilized Factor VIII. However, at that time they did not know whether the presence of antibodies to HIV could also lead to the development of pulmonary hypertension.

As subsequent non-hemophiliac cases were described, suspicion that the development of pulmonary hypertension may relate directly to HIV infection was established. In a state-of-the-art review, for example, Mette et al. (7) could not demonstrate direct HIV infection within the pulmonary vascular endothelium, using advanced techniques such as electron microscopy, immunohistochemistry, DNA *in situ* hybridization and polymerase chain reaction in lung tissue obtained from two patients. The authors postulated that HIV-1 might play a role in the pathogenesis of PH through the release of a variety of mediators associated with retroviral infection, rather than by direct endothelial infection itself.

In a more recent publication, Humbert et al. (8) demonstrated that platelet-derived growth factor (PDGF) activity (a well-known stimulator of fibroblast and smooth muscle cell proliferation) was elevated in the lung biopsies of patients with pulmonary hypertension, irrespective of their underlying state of HIV seropositivity. Interestingly, however, they did not find similar elevations of PDGF activity in HIV-positive individuals without overt PH. These authors also did not identify HIV-1 p24 antigenemia and HIV-1 *gag* RNA in the pulmonary arteries with immuno-histochemistry and *in situ* hybridization, techniques similar to those employed earlier by Mette et al.

Several other mediators aside from the p24 antigen may be implicated in the development of PH in HIV-infected individuals. For example, an article by Ehrenreich et al. (9) reports that the envelope glycoprotein, GP-120, is a potent stimulator of the secretion of endothelin-1 (ET-1). ET-1 is produced from macrophages in a concentration-dependent fashion and is well known to be a potent vasoconstrictor. In addition, the same authors demonstrated a chronically increased expression of the ET-1 gene in the circulating monocytes of HIV-infected patients. An autoimmune etiology has also been implicated as a possible causative factor in the development of PH in patients with HIV. Thus far, studies have demonstrated that anticardiolipin IgM and anti-SS-B have been significantly elevated in patients with HIV-PAH compared to HIV patients without PH (10). However, it remains unclear with this sparse data that the autoimmune phenomenon plays a role in the development of PH.

Interestingly, the fact that only a small percentage of HIV-infected patients will actually develop HIV-PAH suggests that certain predisposing factors are necessary for the development of PH in these patients. Tending to confirm this theory, a study by Morse et al. (28) found that there were significant increases in the frequency of human leukocyte antigen (HLA) class II, HLA–DR6 (DRB1*1301/2 subtype) and of HLA-DR52

(DRB3*301 subtype) in patients with HIV-PAH, as compared to a cohort of 128 HIV negatives and 97 HIV positives without PH. The same HLA-DR6 subtype has also been associated with diffuse infiltrative lymphocytosis syndrome (DILS), previously reported as the CD8 lymphocytic host response HIV-1 infection. Although germ-line bone morphogenetic protein receptor-2 (BMPR2) gene mutation was identified as one cause of both familial and sporadic IPAH including PH patients exposed to fenfluramine derivatives, it was not found in a study of 19 patients with HIV-PAH by Nunes et al. (11).

There is an apparent need for more data and research on this particular aspect of the disease process.

Pathology

The histopathologic findings in HIV-PAH are similar to those of IPAH. These include the development of plexogenic pulmonary arteriopathy, thrombotic arteriopathy and pulmonary veno-occlusive disease, of which plexogenic pulmonary arteriopathy remains the most common finding (Fig. 1; 4). Plexogenic lesions are characterized by medial hypertrophy with concentric intimal proliferation. Mehta et al. report that among the available histopathologic findings from 46 patients, 78% showed plexogenic pulmonary arteriopathy, 11% developed medial hypertrophy and intimal fibrosis without plexiform lesions, and pulmonary veno-occlusive disease was noted in 7% (5). Thrombotic pulmonary arteriopathy remained the least frequent identified lesion, in 4% of the patients.

Clinical Features and Natural Course of the Disease

As stated earlier, the clinical course and progression of PH in HIV-infected individuals is not correlated with the stage of HIV infection or associated with the progression of the disease. The diagnosis of HIV-PAH should therefore only be entertained once all other known etiologies for pulmonary hypertension have clearly been excluded. In patients with HIV and/or AIDS, pulmonary hypertension is known to be more rapidly progressive than in IPAH, with a mean length of time from onset of symptoms to diagnosis of 6 and 30 months, respectively. Many of the known symptoms and signs of HIV-PAH result from right ventricular dysfunction, an etiology that is no different from that of patients with classical IPAH. The most common presenting symptom is progressive dyspnea (85%), followed by pedal edema (30%), non-

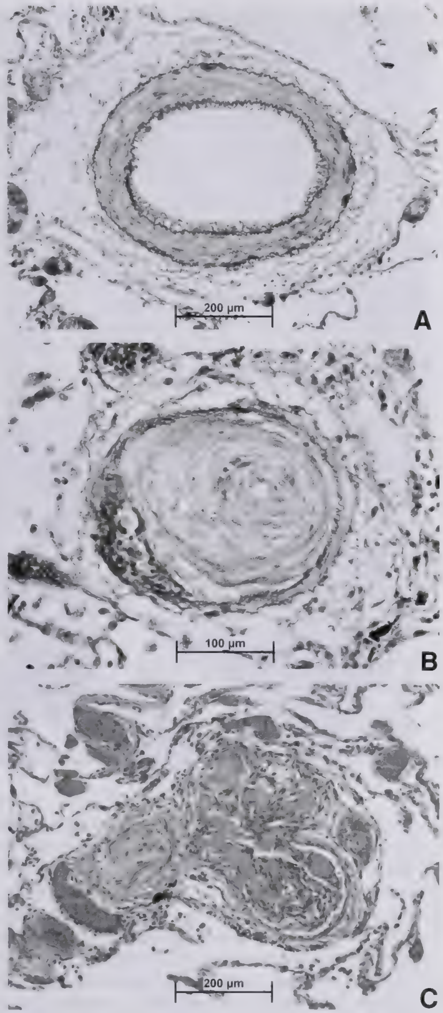

Fig. 1. Photomicrographs of muscular pulmonary arteries from a 43-year-old man with HIV-PAH. (**A**) Medial hypertrophy. (**B**) Concentric laminar intimal fibroelastosis. (**C**) Plexiform lesion. (A and B, Verhoeff-van Gieson; × 50 and × 100, respectively. C, Hematoxylin-eosin; × 50.) (Courtesy of Dr. William D. Edwards, Division of Anatomic Pathology, Mayo Clinic.)

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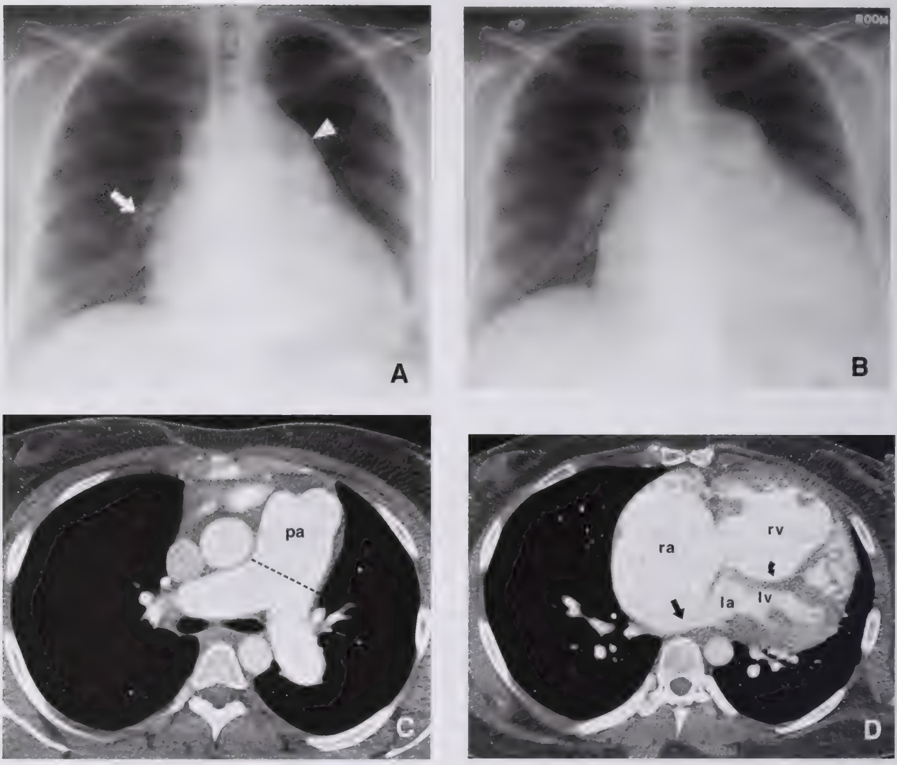
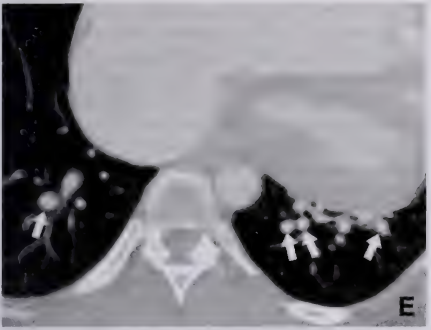


productive cough (19%), fatigue (13%), syncope or near syncope (12%), and chest pain (7%) (4). Relevant physical signs include an increased pulmonic component of second heart sound (P2), a right ventricular heave appreciated on the precordium, and the presence of the systolic murmur of tricuspid regurgitation. In advanced cases, peripheral edema, ascites and hepatomegaly from overt right heart failure may all be present (29).

Patients with pulmonary hypertension can also be functionally classified by using the NYHA classification (12). It is important to mention that no study to date has demonstrated a significant correlation between pulmonary arterial systolic pressure (PASP) and CD4 cell count. The mean CD4 count from one series (27) in patients detected with HIV-PAH was 300 ± 250 cells/mm^3. A review of PASP measures in these individuals revealed a significantly higher PASP in patients with AIDS than in non-AIDS patients (mean PSAP = 85.4 ± 17 mm Hg vs. 71.8 ± 15 mm Hg, 95% CI: 2.98–24.22).

The plain chest X-ray commonly shows cardiomegaly (72%) and prominence of the pulmonary arteries (71%) with clear lung fields. An electrocardiogram frequently reveals nonspecific signs of right ventricular hypertrophy (67%), right atrial abnormality and right axis deviation. In terms of transthoracic echocardiography, findings include right heart chamber enlargement (98%), tricuspid regurgitation, and paradoxical septal motion abnormalities (Fig. 2; 30). Right heart catheterization (RHC) is the standard for confirming the diagnosis of pulmonary hypertension and for evaluating the hemodynamic status and the response to treatment. As reviewed by Mehta et al. (5), mean ± SD of PASP was 67 ± 18 mm Hg in patients with HIV-PAH (n = 116). The pulmonary arterial diastolic pressure (PADP) was 40 ± 11 mm Hg (n = 39) with a pulmonary vascular resistance (PVR) of 983 ±



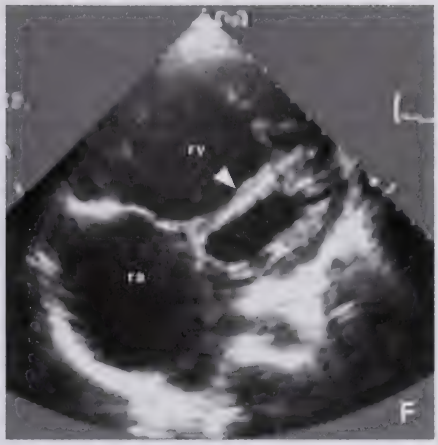


Fig. 2: Interior views of a 28-year-old woman in whom PH was the first manifestation of HIV infection. **(A)** Posteroanterior chest radiograph reveals marked cardiomegaly and an enlarged pulmonary trunk (arrowhead). The right interlobar artery (arrow) measures 21 mm in transverse diameter. **(B)** Posteroanterior chest radiograph obtained 5 years later shows interval progression of the cardiomegaly. **(C–E)** Electron-beam CT pulmonary angiograms (130 keV, 633 mA, 3-mm collimation, 0.2-second exposure). **(C)** Transverse view at the level of the bifurcation of the pulmonary artery (window width, 500 HU; window level, 40 HU) shows enlargement of the main pulmonary artery (*pa*), which measures 43 mm in transverse diameter (dashed line). **(D)** Transverse image obtained at a lower level (window width, 500 HU; window level, 40 HU) shows dilatation of the right ventricle (*rv*) and right atrium (*ra*) and reversal of the interatrial (straight arrow) and interventricular (curved arrow) septa. Simultaneous opacification of the right and left cardiac chambers is noted. *lv* = left ventricle, *la* = left atrium. **(E)** Segmental artery-to-bronchus ratios greater than 1 (arrows) in the lower lobes can be observed on this transverse image obtained at a lower level (window width, 1,400 HU; window level, 300 HU). **(F)** A four-chamber view from an echocardiogram shows right ventricular (*rv*) and right atrial (*ra*) dilatation. Paradoxical movement of the interventricular septum (arrowhead) was observed at real-time imaging.

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420 dyne·s·cm^{-5} (n = 29). Pulmonary function tests (PFTs) have revealed a mildly restrictive pattern with variable reductions in diffusing capacity, another phenomenon that has not been shown to correlate with the severity of PH.

Treatment Modalities and Therapeutic Considerations

It is important to remember that HIV-PAH is a progressive disease for which there is no cure. No study has yet established a single agent of choice for its treatment, even though considerable progress has been made over the past few years.

The most commonly used agents in the treatment of HIV-PAH remain PAH-specific therapy and antiretroviral medications themselves.

Stricker et al. reported two cases of HIV-PAH with NYHA class IV dyspnea treated with aerosolized prostacyclin (13). Acute responses of reduction of mean pulmonary arterial pressure (PAP) from 73 to 62 mm Hg and 53 to 47 mm Hg, reduction of PVR from 1093 to 945 dyne.s.cm^{-5} and 860 to 837 dyne.s.cm^{-5}, respectively, were noted. Based on these initial promising results, one patient was subsequently initiated on long-term treatment with inhaled epoprostenol and the other initiated on long-term inhaled iloprost treatment. After a mean of seven months' follow-up, both patients demonstrated sustained reduction of PAP and improvement of symptoms (NYHA class IV to class II), as demonstrated by increasing walking distances on treadmill tests and improvement of NYHA functional status.

In yet another prospective study (14), six patients with severe HIV-PAH were treated with continuous intravenous epoprostenol infusions. This trial demonstrated a significant acute reduction of mean PAP (16.4%) and PVR (32.7%). The mean cardiac output was also found to be significantly increased (36.9%). After one year of follow-up, mean PAP and PVR had decreased by 21.7% and 54.9% ($p < 0.05$) respectively, and the mean cardiac output had increased by 51.4%($p < 0.05$) when compared to baseline values. All patients were noted to have developed an improvement in their NYHA functional class. Further improvement and maintenance of hemodynamics was demonstrated in three patients at two years and one patient at 40 months. These sustained improvements are consistent with the trial conducted by Nunes et al. (11). However, there are some concerns about long-term epoprostenol infusion, e.g., lack of pulmonary selectivity, tachyphylaxis requiring dose escalation, inconvenient drug delivery system, catheter-related sepsis and inadvertent drug interruption, which may lead to death in 15 – 30 minutes. Other adverse effects typical of prostacyclin administration include jaw pain, intermittent headache, and flushing, especially with dosage increases.

Given the complicated technique associated with long-term epoprostenol infusion, the long-term effects of inhaled iloprost were studied (15). Eight patients with severe HIV-PAH (NYHA class III and IV) were monitored for hemodynamic responses with right heart catheterization while receiving oxygen, short-term nitric oxide (NO) inhalation challenges, and iloprost inhalation.

The acute vasodilatory potency was greatest for iloprost > NO > oxygen, with a maximum reduction (mean ± SEM) in PVR of 30.6 ± 3.1% ($p < 0.001$), 5.9 ± 3.9% and –0.6 ± 3.9% respectively. Iloprost was also noted to produce a significant increase in the cardiac index by 20.9 ± 8.9% ($p < 0.01$), while simultaneously beneficially decreasing the PVR to systemic vascular resistant (SVR) ratio, a fact that indicates preferential pulmonary vasodilatation. It is interesting to note, however, that none of the patients in this study cohort were found to be "NO-responders." NO response has been widely accepted as a screening tool that helps in identifying patients who will respond favorably to long-term treatment with high doses of oral calcium channel blockers in IPAH.

Four of the eight patients in the study mentioned above underwent chronic therapy with inhaled iloprost over six months without significant changes in parameters of their HIV infection (as measured by CD4 count and viral load). However, all of these patients demonstrated clinical improvement of NYHA functional capacity, and their average 6-minute walking distance increased from 331 ± 21 m to 417 ± 40 m ($p = 0.063$), with a decrease in average PVR from 1,402 ± 324 dyne.s.cm^{-5} to 772 ± 89 dyne.s.cm^{-5} ($p = 0.065$).

The effect of calcium channel blockers on the course of HIV-PAH remains unclear, though they are known to be efficacious in a very selective group of IPAH patients. In one small study, for example, none of five tested patients with known HIV-PAH responded to calcium channel blockers, and four of them experienced intolerable side effects necessitating discontinuation of therapy (31).

Bosentan, an endothelin-1 receptor antagonist of proven efficacy in the treatment of primary pulmonary arterial hypertension (32), has also recently been shown to have clinical benefits in a nonrandomized clinical trial of 16 patients with HIV-PAH and in NYHA class III-IV, in terms of 6-minute walk distance (+91 ± 60 m, $p < 0.001$), NYHA class (14 patients improved), hemodynamics (cardiac index: +0.9 ± 0.7 L/minute/m^2, $p < 0.001$), Doppler echocardiographic variables, and quality of life at 16 weeks' observation (33).

Sildenafil, a specific phosphodiesterase isoform (PDE5) inhibitor, given orally, has been reported to cause a persistent reduction of PAP. It has been clinically demonstrated to improve dyspnea and exercise tolerance (16 – 18).

There is no current trial objectively evaluating the effect of antiretroviral therapy on the progression of HIV-PAH. In a prospective study with a median follow-up of 13 years, Opravil et al. observed that five out of eight patients who had significantly stable and decreasing estimated PASP were receiving regular antiretroviral therapy (10). Interestingly, four out of five patients with increasing estimated PASP were not receiving any antiretroviral therapy. The difference between last and first pressure gradient was +19.0 mm Hg and – 3.2 mm Hg in the untreated and treated groups, respectively ($p = 0.026$). A retrospective study using highly active antiretroviral therapy (HAART), including the newer protease inhibitors, failed to demonstrate any significant benefit on the clinical course of PH. In fact, two patients in this study, who had low viral loads and were treated with HAART, demonstrated an accelerated course of PH with worsening PASP (34). Conversely, a study of a subgroup of 47 patients with HIV-PAH in the Swiss HIV Cohort Study found that patients who received HAART had a significantly decreased median right ventricular systolic pressure over right atrial pressure gradient (– 21 mm Hg), compared with patients who received 2 nucleoside analog reverse-transcriptase inhibitors (– 3 mm Hg) and those who did not receive antiretroviral therapy (+25 mm Hg) (35).

There is not enough supporting evidence for the use of anticoagulant in HIV-PAH, although *in situ* thrombosis is occasionally found.

Prognosis

The prognosis of HIV-PAH remains poor despite clinically significant advances in therapy. The development of PH and low CD4 counts are the two most commonly associated independent predictors of death in HIV-infected patients (10). In one study of 131 cases of HIV-PAH, two thirds of the deaths in HIV-PAH were due to direct consequences of PH itself, such as right-sided heart failure, cardiogenic shock and sudden cardiac death (5). Nunes et al. (11) studied the prognostic factors for survival among 82 patients with HIV-PAH. They also found that about two thirds of total mortality was caused by PH itself (5). The overall survival rate at one, two and three years were 73%, 60%, and 47%, respectively. Predictably, survival was dramatically worse in patients in NYHA class III-IV, when compared to patients with NYHA class I-II ($p < 0.0001$) in subgroup analysis. This fact helps emphasize the role of NYHA functional class placement as a major indicator of prognosis in HIV-PAH. The authors also specifically analyzed for the factors associated with mortality in the subgroup of patients in NYHA class III-IV. They demonstrated that CD4 count of more than 212 cell/mm^3, use of combination antiretroviral therapy (CART) and treatment with epoprostenol were significantly related to a decreased risk of death. However, only CD4 count was shown to be an independent predictor of survival in multivariate analysis. CART and epoprostenol therapy were strongly linked with positive outcomes. The survival was worse in NYHA class III-IV patients who were treated with CART only, compared with those receiving CART and epoprostenol.

Summary

Physicians should be aware of possible pulmonary hypertension in patients with HIV infection who present with progressive shortness of breath and/or symptoms or signs of right-sided heart failure, as this condition increases morbidity and mortality. We recommend screening of these patients with transthoracic echocardiography. HAART may be considered for any HIV-infected patient with pulmonary hypertension, regardless of CD4 counts or viral load.

Despite major advances over the past few years, treatment options for HIV-PAH remain limited and unsatisfactory. Varieties of PAH-specific treatments have been explored, but still require larger trial(s) for better evaluation of the effects on clinical outcomes.

The prognosis for HIV-PAH remains predictably grim, with higher mortalities among patients with higher NYHA functional class. Earlier screening and a more effective application of HAART to HIV-infected individuals, in conjunction with the development of more clinically efficacious PAH-specific treatments, offer hope that the burden of disease may be reduced. Further large-scale clinical and experimental studies are clearly needed to help us better understand and manage this complex pathophysiologic disease state.

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Splenic Abscess in a Patient with Wegener's Granulomatosis Treated with Laparoscopic Splenectomy

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Abstract

Splenic abscess complicating Wegener's granulomatosis (WG) has not been previously described. We report the occurrence of a splenic abscess in a 45-year-old white male suffering from WG. The patient presented with persistent fever and abdominal pain. Magnetic resonance imaging showed two splenic cystic lesions. Differential diagnosis was splenic hematoma or abscess. The patient underwent diagnostic laparoscopy and laparoscopic splenectomy. Pathology revealed a centrally located cavity full of pus and necrotic material. Although there were no signs of active vasculitis, all other histological features were compatible with WG. The patient had an uneventful postoperative course and his disease is in remission. Laparoscopic splenectomy appears to be a safe procedure, but its impact on the management of splenic abscess needs to be determined further.

Key Words: Wegener's granulomatosis, splenic abscess, laparoscopic splenectomy.

Introduction

WEGENER'S GRANULOMATOSIS (WG) is a disease characterized by necrotizing granulomatous vasculitis of small and medium-sized arteries (1). Most frequently it involves the upper and lower respiratory tract and the kidneys and has a wide range of manifestations with a broad spectrum of severity (1). Survival in WG increased dramatically after the introduction of cyclophosphamide and glucocorticoids (median survival >21 years) but often with considerable disease- and treatment-related morbidity (2, 3).

Spleen involvement in WG is not unusual but is rarely diagnosed during life and is probably underreported (4, 5). Spleen pathology in affected patients includes infarction and necrosis with central arteritis, hemorrhage, rupture, capsule adhesions, splenomegaly and function impairment (4–7). There has been no previous report of a splenic abscess in WG.

We present a patient with Wegener's granulomatosis who underwent laparoscopic splenectomy for a splenic abscess.

Case Report

A 36-year-old white male was admitted in 1996 because of hemoptysis. Thoracic computed tomography (CT) revealed a round cavity with thick walls in the middle lobe of the right lung. There was no lymphadenopathy, and tests for specific infections (tuberculosis, parasitosis) were negative. An open lung biopsy showed granulomatous necrotic inflammation consistent with Wegener's granulomatosis. The patient was placed on methotrexate and folic acid for three years. In 1997 he had an episode of lower gastrointestinal bleeding due to an angiodysplasia of the cecum. A contrast-enhanced CT scan of the abdomen showed a hypodense multilobular area in segment V (Couinaud classification) consistent with a granuloma from WG.

In March 2005 the patient gradually developed discomfort and persistent pain of the left upper quadrant, which worsened at deep inhalation. Subsequently, he developed pain in his proximal interphalangeal joints, knees and ankles and had lost 4 kg in weight over three weeks. His temperature

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was constantly between 37.5 and 37.8°C. On physical examination he appeared ill, with a temperature of 38°C, a pulse of 110 beats per minute and a blood pressure of 115/75 mm Hg. He had severe tenderness over the left upper quadrant and splenomegaly. The hemoglobin was 9.7 g/dL, the white cell count 14,500/mm^3 and the platelet count 212,000/mm^3; the prothrombin and partial-thromboplastin times were normal. The erythrocyte sedimentation rate (ESR) level was 95 mm/hour and the C-reactive protein (CRP) level was 102 mg/L. Levels of C_3, C_4, p-antineutrophil cytoplasm autoantibodies (p-ANCA), c-ANCA were normal; rheumatoid arthritis (Ra) and antinuclear antibody (ANA)-tests were also normal. The lupus anticoagulant and anticardiolipin antibodies were negative. Chest X-ray was unremarkable. Chest CT scan revealed the known lesion in the middle lobe of the right lung. A contrast enhanced CT and a magnetic resonance imaging (MRI) scan of the abdomen (Fig. 1) showed two non-enhancing splenic cysts (6.5 cm and 4.2 cm) and a focal lesion in segment IV consistent with the known granuloma. A transesophageal echocardiogram failed to detect cardiac sources of emboli.

The differential diagnosis was splenic hematoma or abscess associated with WG. Administration of methylprednisolone (500 mg IV per day for three days) and cyclophosphamide (2 mg/kg per day, orally) was begun. Methylprednisolone was continued at 48 mg per day orally and trimethoprim and sulfamethoxazole were started after three days.

Over the next two months the patient had constant low-grade fever with minimal improvement. Abdominal imaging showed that the splenic lesions were unchanged. A diagnostic laparoscopy was performed.

Operative Findings

The spleen was enlarged and densely adherent to the lateral abdominal wall, the diaphragm and the stomach. Two cystic lesions were identified at the splenic hilum. There was no ascites, gross lymphadenopathy or other intra-abdominal pathology. A laparoscopic splenectomy was performed. Biopsies were taken from the lesion in the right lobe of the liver.

The patient had an uneventful postoperative course and was discharged on the fourth postoperative day. Six months later, he was asymptomatic with normal levels of ESR and CRP, and his disease was in remission.

Histopathology

Gross Findings

The patient's spleen measured 10×11.4×4 cm with a weight of 260 g. In sectioning, there was a central cavity measuring 4 cm containing pus and necrotic material.

Microscopic Findings

Foci of granulomatous inflammation and thrombosed vessels were found peripherally to the necrotic area (Figs. 2 and 3). Small arteries throughout the spleen had thickened walls and lumen stenosis (Fig. 4). Some small arteries had eosinophilic degeneration and chronic inflammation. Thrombosed vessels and small foci of ischemic necrosis were found distally to the necrotic cavity. Histochemistry did not reveal any microorganisms.

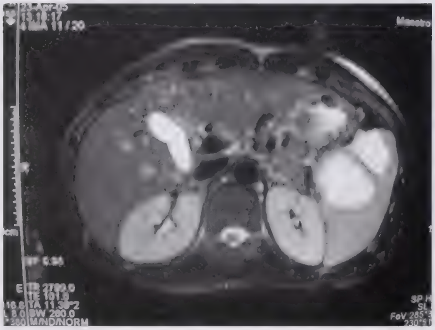

Fig. 1. Abdominal MRI scan.

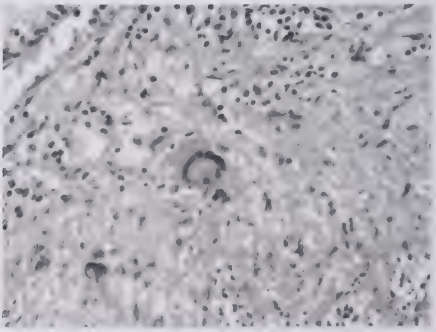

Fig. 2. Giant cells at the periphery of the necrotic area in the splenic parenchyma (H&E × 200).

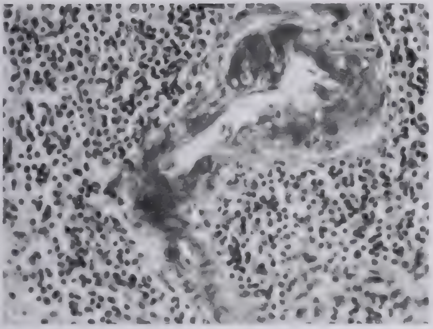

Fig. 3. Regressive vascular necrosis: PAS + material on the vascular wall (PAS × 200).

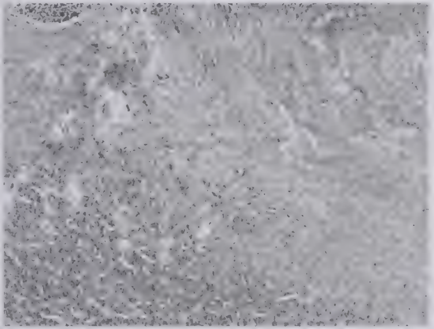

Fig. 4. Palisading histiocytic inflammation around foci of splenic necrosis (H&E × 100).

Discussion

Manifestations of splenic involvement in WG include splenomegaly, splenic vasculitis, rupture, infarction, necrosis and impaired splenic function (4–10). Splenic abscesses are a recognized complication of Felty's syndrome, rheumatoid arthritis, systemic lupus erythematosus and polyarteritis nodosa (7), but there have been no previous reports describing the occurrence of a splenic abscess in WG.

Splenic abscesses occur predominantly as a result of hematogenous spread from a septic focus (usually endocarditis) or secondary to immunosuppression (11, 12). No apparent etiology (e.g., infectious, hematologic, neoplastic) for a splenic abscess was found in the described patient. The pathogenesis remains obscure, but there are reports of aseptic splenic abscesses in other diseases associated with circulating ANCA, such as inflammatory bowel diseases (13, 14).

Although there were no signs of active vasculitis in the pathology examination, all other histologic features (palisading granuloma around foci of necrosis, small vessel involvement) (15) were compatible with WG. It should be noted that the fundamental disease mechanism in WG is connective tissue "necrobiosis" (severe involvement of collagen and other mesenchymal tissues) and not vasculitis (15).

Diagnosis of a splenic abscess can be difficult, because the symptoms are nonspecific and can vary widely. Fever, left upper quadrant pain, nausea/ vomiting and splenomegaly with leucocytosis are the most common signs and symptoms associated with a splenic abscess (12, 16). Contrast enhanced CT scan and MRI are the most sensitive imaging techniques (12). This patient had the classic symptoms (with radiological imaging) suggestive of a splenic abscess.

Minimally invasive surgery is now the procedure of choice for elective splenectomy. Significant splenomegaly (length > 22 cm or weight >700 g) is considered a relative contraindication to laparoscopic resection due to the difficulty in manipulation and the potential for significant hemorrhage (17). Hand-assisted laparoscopic splenectomy can be used in such cases, as it offers the advantages of minimally invasive surgery while allowing safer resection (17).

Splenectomy is the treatment of choice for splenic abscess (11, 12). Splenic resection is the most effective and definitive procedure for the majority of patients, although percutaneous drainage is very helpful in carefully selected cases (18). Carbonell et al. showed that laparoscopic splenectomy is a safe and effective method for treating splenic abscesses (16), as in the case of this patient. Although the number of patients in their study was small, there was no morbidity or mortality and they had shorter hospital stays compared with the open splenectomy cohort (16). The impact of minimally invasive surgery on the management of splenic abscess needs to be investigated further.

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A Case Report of Fatal Oral Ingestion of Resorcinol

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Abstract

Resorcinol is a pharmaceutical agent used topically in dermatological treatments for acne, eczema, psoriasis and related skin conditions. Although there are a few studies that indicate chronic toxic effects of resorcinol on humans after topical application, information on the effects of resorcinol in acute poisoning after oral ingestion is limited. Thus, we wish to report the clinical and laboratory findings of a patient who was admitted to our emergency department (ED) after inadvertent oral ingestion of resorcinol and later died, as well as the patient's autopsy findings. The major clinical and laboratory findings were unconsciousness, respiratory failure that required mechanical ventilation, generalized tonic-clonic seizures, leukocytosis and severe metabolic acidosis. In the blood sample taken at the autopsy, a high level of methemoglobin was found. In the serum, resorcinol was revealed by gas chromatography-mass spectrometry. It can be concluded that the basic approach to patients with resorcinol poisoning should include initial stabilization of the patient by supporting the airway, respiration and circulation, and treating complications such as seizures or metabolic acidosis in the ED, as soon as possible after oral ingestion.

Key Words: Resorcinol, oral ingestion, toxicity, fatal.

Introduction

Resorcinol is a chemical used in photography and tanning, and in the manufacture of tires and other rubber products; it is a component of adhesives, hair dyes and cosmetics. Resorcinol is also a pharmaceutical agent used topically in dermatological treatments for acne, seborrhoea, eczema and psoriasis. It has been found in roasted barley, canned molasses, coffee, cigarette smoke, effluents from production of coal tar products, and waters from aquifers rich in coal and shale deposits (1).

Resorcinol is rapidly and completely absorbed following oral exposure. Studies of oral application have reported rapid absorption and excretion, mainly in the form of glucuronide and sulfate conjugates. These studies indicate rapid and extensive first-pass metabolism of resorcinol following absorption into portal blood flow (1). Resorcinol may be absorbed through the skin or the lungs. The threshold limit value for occupational exposure is 10 ppm (45 mg/m^3) in air as a time-weighted average, with a short-time exposure limit of 20 ppm (90 mg/m^3) (2).

Although there are a few studies that indicate chronic toxic effects of resorcinol on humans after topical application (3 – 5), information on the effects of resorcinol in acute poisoning after oral ingestion is limited. Thus, we wish to report the clinical and laboratory and autopsy findings of a patient who had been admitted to our ED after an inadvertent oral ingestion of resorcinol.

Case

At 12:10 PM, a 46-year-old woman was admitted to the ED of Uludag University Medical Faculty Hospital, Bursa, Turkey with loss of consciousness and convulsions, shortly after having a glucose challenge test because of a recent high blood glucose level. Just before her transfer to our service, she had been intubated because of persistent convulsions and coma.

On her arrival, her pupils were isocoric and miotic, pupillary light reflexes were negative bilaterally, blood pressure was 110/70 mm Hg, pulse rate 120 beats/min, and temperature was 37°C. The Glasgow Coma Scale reading was 3 points. She

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had generalized tonic-clonic seizures and negative deep tendonal reflexes. She was intubated and had spontaneous but inefficient respiration. Systemic physical examination revealed no pathology. ECG demonstrated normal sinus rhythm with a pulse rate of 120. Gastric lavage with activated charcoal (1 g/kg) was performed, since we did not know the exact time of oral ingestion, and it had not been performed in the hospital where she was originally admitted. We obtained a complete blood count: white blood cells 42.900/mm^3, hemoglobin 11.8 g/dL, hematocrit 35.4%, platelets 611,000/mm^3, glucose 329 mg/dL, electrolytes (Na 149 mEq/L, K 4.9 mEq/L). We also did a urinalysis (pH 6.5, protein 30 mg/dL, glucose 250 mg/dL, negative results of ketones, blood, bilirubin and nitrite), and baseline renal and liver measurements (urea 17 mg/dL, creatinine 1.2 mg/dL, aspartate aminotransferase (AST) 47 IU/L, alanine aminotransferase (ALT) 23 U/L). The first arterial blood gas levels were as follows: pH 7.021, pCO_2 60.5 mm Hg, pO_2 45.5 mm Hg, HCO_3 15.3 mmol/L, base excess (BE) 16.2 mmol/L. After resuscitation, in order to eliminate the possibility of brain lesions, a cranial computerized tomography scan was performed. It did not show any pathological finding.

We were informed that resorcinol (Rezorsine, 75 g, EGAS A.S. Ankara, Turkey) had been given to the patient by a pharmacist instead of glucose, which had been prescribed for a 75 g glucose challenge test. She had been admitted to our ED 2 hours after ingestion.

The patient was supported by mechanical ventilation, due to her respiratory insufficiency. For treatment of her seizures, diazepam IV was administered, and due to recurrent seizures after diazepam, phenytoin infusion was started. We monitored acid-base balance closely. To treat metabolic acidosis, $NaHCO_3$ IV infusion was administered under arterial blood gas control. A central venous line was established and a Foley catheter inserted. The central venous pressure was 4 cm H_2O. Liquid support was continued with central venous pressure observation. Diuresis was performed in order to enhance resorcinol elimination from the plasma via urine. After the patient was transferred to an intensive care unit, hypotension, pulmonary edema and oliguria occurred. Metabolic acidosis was not corrected in spite of the treatments. Cardiopulmonary arrest occurred, although cardiopulmonary resuscitation was performed; as a result, the patient died at 6:00 PM.

A medico-legal autopsy was performed at the Morgue Department of the Bursa branch of the Council of Forensic Medicine of Turkey. At macroscopic examination, there were nonspecific findings such as diffuse pulmonary edema, and evidence of the medical treatment, such as activated charcoal in the stomach. Microscopic examination revealed pulmonary edema, renal congestion, an eosinophilic substance in renal cortical tubular lumens, and hyperemia in all organs. The Toxicology Department found neither alcohol in her blood nor toxic substances in her tissue samples. Screening and identification of drugs (amphetamines, barbiturates, benzodiazepines, cannabinoids, opiates) in the urine and blood samples were also performed by cloned enzyme donor immunoassay (CEDIA), and none of them were found. In her blood, 10% methemoglobin was estimated by CO-oximetry. However, in her serum, and in the plastic cup that she had used, resorcinol was revealed by gas chromatography-mass spectrometry.

Discussion

The toxic effects of resorcinol and treatment are similar to those of phenol. Resorcinol, with a pleasant scent and a sweetish taste, is used to treat acne and similar skin conditions (2). Kim et al. reported that, following oral administration, resorcinol was readily absorbed from the gastrointestinal tract, rapidly metabolized, and excreted by male and female rats. In both sexes, most of the dose of resorcinol (more than 90%) was excreted in the urine within 24 hr after oral administration of 112 mg/kg, indicating little potential for bioaccumulation in animal tissues (6). Pharmacokinetic data on resorcinol were obtained in rat studies (2).

The human data consist of anecdotal and case reports and several epidemiology studies. The anecdotal reports refer to acute poisoning, often through attempted suicides. The case reports document sensitization reactions in occupationally exposed persons and thyroid effects in persons using dermatological ointments containing resorcinol. The epidemiology studies have focused on effects of resorcinol in occupationally exposed persons and in populations living in geographic regions where drinking water contained resorcinol and other phenolics derived from natural sources (1).

Resorcinol is of moderately acute toxicity. Acute oral lethal dose 50% (LD_{50}) values of 980 mg/kg and 300 mg/kg have been reported for rats. Death was associated with convulsions, salivation, dyspnea, emaciation, and hyperemia of the gastrointestinal tract. A single-dose dermal LD_{50} value of 3360 mg/kg has been reported in rabbits (1). The lowest lethal dose (LDL_0) of resorcinol in humans has been reported as 29 mg/kg (2). While the LDL_0 was 2.6 g in our patient (90 kg), the ingested amount was 75 g, which could have caused an avoidable death.

In acute exposure, concentrated phenol is extremely corrosive and may cause oral, esophageal, and gastric burns following ingestion. Systemic manifestations of toxicity may include nausea, vomiting, diarrhea, dyspnea, methemoglobinemia, hypothermia, tachypnea, pallor, and profuse sweating. Hypotension and tachycardia are commonly reported (7). While our patient had only sinusal tachycardia on arrival, hypotension occurred a few hours after. Tachypnea is commonly reported; pulmonary edema and bronchospasm may also occur. Respiratory arrest occurred 30 minutes after ingestion of 26.7 grams of phenol in one case. A short time after ingestion, our patient's respiration became insufficient and she had to be intubated. Her autopsy also revealed diffused pulmonary edema.

In neurologic acute exposure, initial central nervous system excitations, including seizures, are commonly followed by central nervous system depression ranging from lethargy to coma and death (7, 8). There have been reports of methemoglobinemia and acute poisoning, in some cases with fatal outcome, in children, even when limited areas were exposed to resorcinol (3). Seizures were observed in our patient in her acute exposure after oral ingestion. A major antiepileptic drug infusion was started due to the failure to stop the seizures, by administrating diazepam. In the blood sample taken at the autopsy, a high level of methemoglobin was found.

Pathology reported for humans includes marked siderosis of the spleen and marked tubular injury in the kidney, fatty changes and edema of the liver, degenerative changes in the kidney, fatty changes of the heart muscle, moderate enlargement and pigmentations of the spleen, and edema and emphysema of the lungs (9). Autopsy findings in our case displayed a similarity to those noted above, especially for the kidney and lungs.

In Turkey, resorcinol is bought in kilogram bulk and then packed into small plastic packets and labeled, as is the case with glucose in some pharmacological products; this task is done by nonspecialized workers employed by the pharmacists. The similarity in packets and employee carelessness led to this medication error. In an earlier case, also in Turkey, resorcinol was mistakenly administered instead of glucose in a glucose oral test for a pregnant woman. This patient was discharged fifteen days after being admitted to the hospital, but her fetus was lost. The main reason why our patient died is that she came to our hospital too late (2 hours after oral ingestion).

According to the legal system of our country, all cases of death by poison are recorded as unnatural deaths and are subject to medico-legal autopsy. Thus, medico-legal autopsies are one source of reliable data on fatal poisoning cases. The punishment for responsibility for the situation in our case is stipulated in the Turkish Penal Code: if any person causes someone to die through an incautious and inattentive act, the guilty person shall be imprisoned for three to six years.

This is the first case report on fatal oral resorcinol poisoning in a woman, with clinical and laboratory findings along with autopsy findings. It suggests the need to take better precautions, such as labeling items more carefully in pharmacy, selling different items in plastic bags of different colors and employing better trained and better informed persons in the pharmacy, etc., for preventing inadvertent oral ingestion of resorcinol. However, bearing in mind that there is neither an antidote nor a specific therapy for resorcinol poisoning other than the supportive treatment, the present report suggests that the basic approach to patients with resorcinol poisoning should include initial stabilization of the patient by supporting the airway, respiration and circulation, and treatment of any complications such as seizures or metabolic acidosis in the emergency department as soon as possible after inadvertent oral ingestion. Then the patient should be transferred to the intensive care unit, to further control any life-threatening complications, as well as to observe the patient closely.

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Managing the Blue Man:

Multiple Traumas Involving a Paint-Carrying Truck

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Abstract

Introduction: This report describes the difficulty in evaluating a patient with multiple traumas because he was covered with paint poured from a truck in a car accident. Cleansing with paint thinner and isotonic saline solution was necessary.

Case Report: A 29-year-old male patient was admitted to the emergency department following the collision of his car with a paint-carrying truck. His head, face, neck and hands were covered with a cyan-blue oil paint, and bloody "paint mud" covered all frontal and occipital areas of the scalp. Abdominal guarding was identified. A rapid cleansing with normal saline solution (0.9% NaCl) was attempted in order to expose the lesions of the patient, but it had no effect on the drying paint. The patient's scalp, face and neck were cleaned with paint thinner (60% toluene). The patient was then diagnosed as having a maxillofacial fracture and underwent surgery for open reduction and rigid fixation by plastic and reconstructive surgeons. Thinner was not used for the eyes for fear of further chemical injury. Normal saline removed corneal and conjunctival paint remnants but proved ineffective for cleansing of the eyelids and eyelashes.

Conclusion: Removal of the paint from the skin and the eyes was a prerequisite for the evaluation of the underlying structures. It is difficult to find a cleansing material that can be used effectively and safely in different parts of the body.

Key Words: Multiple traumas, accident, paint, skin cleansing, contaminated wound, eye wounds.

Introduction

Patients with contaminated wounds are not uncommon admissions in an emergency department (ED). Although there is evidence to suggest that wound cleansing is not always necessary for wound care (1, 2), appropriate cleansing of the patient is a must to allow evaluation of underlying structures. This paper reports a patient with multiple traumas complicated by contamination with paint poured from a paint-carrying truck in a car accident, and the patient's evaluation and management with the help of paint thinner and saline solution.

Case Report

A 29-year-old male patient was admitted to the ED of a private hospital following a collision of his car with a paint-carrying truck. On admission, his entire head, face, neck and hands were covered with a cyan-blue oil paint. He had subconjunctival hemorrhage and chemosis on the right eye, and his eyelashes were all covered and stiffened by the paint. He had a linear 3-cm long cut on the left zygomatic area, which was covered by the dry paint, and bloody "paint mud" covered all frontal and occipital areas of the scalp. External ear canals were covered as well, but no hemorrhage was seen. Abdominal guarding was identified on examination. No neurologic deficit or any other abnormality was detected.

A rapid cleansing with normal saline solution (0.9% NaCl) was attempted in order to expose the lesions of the patient, but it had no effect on the drying paint. To remove the paint, it became necessary to use paint thinner (60% toluene), which was identified as the solvent of the paint on the package label. Following consultation with a dermatologist, the patient's scalp, face and neck were cleaned with thinner, which was then washed off with normal saline solution. Reevaluation of the patient revealed edema and ecchymosis of 5 cm in diameter around the right eye and a linear, full-thickness 3-cm cut on the left zygomatic area. The "mud," consisting of blood and paint, was also removed, and no other lacerations or cuts were noted

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in the scalp. A cream, including hydrocortisone in combination with fusidic acid, was then applied in the erythematous areas to avoid a possible contact dermatitis and secondary infection.

Abdominopelvic ultrasonography was normal. Cranial computed tomography revealed fracture in the anterior walls of maxillary sinuses bilaterally, in the left pterygopalatine plate and in the posterior part of the left lamina propecia; hemorrhage in the maxillary sinuses bilaterally, in the anterior and posterior ethmoidal cells and in the left sphenoid sinus; and a small contusion area localized in the periventricular substantia alba in the posterior part of the right nucleus caudatus.

The patient was diagnosed as having a maxillofacial fracture and underwent surgery for open reduction and rigid fixation by plastic and reconstructive surgeons. No lesions of contact dermatitis were observed, and there was no sign of acute neurotoxicity.

In the ophthalmology consultation, oil paint covering the eyelids and eyelashes made the first evaluation difficult. After local anesthetic application and retraction of eyelids, the patient's eyes were irrigated for approximately 30 minutes by isotonic saline solution. Residual substances in the eye were removed by sponge. Thinner was not used for the eyes, for fear of further chemical injury. Normal saline successfully removed corneal and conjunctival paint remnants but proved ineffective for cleansing of the eyelids and eyelashes. At the first examination of the patient, his vision was 7/20 in both eyes, and diffuse punctate epithelial defects were detected on his corneas and conjunctivae. Intraocular pressures were within normal limits and there were no other injuries in anterior and posterior segments. In the first-line treatment, topical cyclopentolate 1% (three times a day), topical ofloxacin (four times a day) and polyvinyl alcohol eye drops (four times a day) were applied. Two days later, ophthalmologic examination was repeated, and it was observed that the oil-painted eyelashes were everted and caused additional epithelial defects on the cornea. Sponges with warm water were applied on the eyelids and eyelashes to soften the stiffened paint, and his eyes were again washed with normal saline solution. (A forceps was used in the unsuccessful attempt to remove some more paint.) The cleaning was also repeated on the following days. Corneal and conjunctival damage resolved on the third day without any additional treatment. Complete removal of paint from eyelids and eyelashes was accomplished by the fifteenth day.

Discussion

Patients with multiple traumas sometimes present in the ED with contaminated wounds. Although there is evidence to suggest that wound cleansing is not always necessary for wound care (1, 2), appropriate cleansing of the patient is necessary for the evaluation of underlying structures. When managing a multiple trauma patient, physical examination is of vital importance in terms of diagnosis, treatment and outcome. To inspect a wound thoroughly, contaminants should be removed and the wounds should be cleaned using normal saline solution whenever possible, as it is harmless and gentle to the tissue (2, 3). Most reports about care of the contaminated wound in the ED focus on wound healing and secondary infection risks. Saline solution and surfactants are suggested media for the cleansing (4). Yet saline solution may not be sufficient to clean the wounds to allow a thorough inspection, as was the case with our patient. And it was necessary to cleanse the wounds to find out the extent of trauma in the tissue itself. Paint thinner (60% toluene) was used to remove the dried cyan-blue paint, because of its solvent properties. Exposure of the skin to thinner has some known untoward effects such as contact dermatitis and neurotoxicity, which can result from chronic repeated exposure (5–7). The risk of contact dermatitis, which may be caused by the paint itself as well, was faced because of the possibility of a life-threatening trauma. Systemic toxicity of thinner was not a concern here, as it was used over the face, which is a small percentage of the total body surface, and thus systemic absorption and toxicity was expected to be minimal. Also, thinner toxicity has been reported to occur in chronic exposure (5–7). Because of the possibility of a life-threatening head trauma and because all risks due to thinner exposure seemed to be of secondary importance, the patient's face was cleansed with paint thinner and then washed with normal saline. Reevaluation of the patient after cleansing revealed ecchymosis around the eyes and the maxillary area, possible indicators of a maxillofacial injury. Although technological advances in radiologic imaging facilitated the diagnosis, the importance of clinical evaluation cannot be overlooked. (A thorough literature search failed to yield any similar paint-cleansing procedure that had employed toluene.)

Corneal and conjunctival injuries following exposure to chemical substances are fairly common emergencies. Industrial materials with acid and alkaline content can cause severe burns and anterior segment injury. These injuries may vary from superficial corneal and conjunctival epithelial defects to severe corneal opacification, or even loss of vision. Exposure time, content of chemical substance (alkaline or acid) and its potency are important factors in determining the level of injury. Any patient referred to the ED for possible chemical exposure should be investigated for the type of chemical substance and its strength. Eyes should be immediately irrigated by physiologic saline solution, and an ophthalmologist should be consulted (8, 9). In this case, the most difficult procedure was cleansing the eyelids and eyelashes from the paint. Unavailability of a non-toxic substance to remove the paint from the eye increased the damage and prolonged the treatment period. Working on this case, we realized that there might not be a safe and effective paint remover for the eyes. Al least we could not identify such a material in the literature.

It was essential to cleanse the skin and eyes of this patient. Removal of the paint was a prerequisite for evaluating the underlying structures. Eye cleansing was necessary to prevent further damage caused by the dried paint in the eyelashes. But it was difficult to find a cleansing material that could be used effectively and safely on different parts of the body. If possible, the product label should be consulted for appropriate cleansing agents.

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Editor's Note

AVE ATQUE VALE

WITH THIS ISSUE OF THE *JOURNAL*, I conclude my term as Editor-in-Chief.

The history of the *Journal* is long and rich, and reflects to some extent the proud history of the institution it represents. It has been published continuously since 1934, and during these 73 years of publication it has had only six editors. I salute my five predecessors: Joseph Globus, M.D. (1934–1952); Solon S. Bernstein, M.D. (1952–1953); Lester M. Tuchman, M.D. (1954–1974); David A. Dreiling, M.D. (1974–1991); and Sherman Kupfer, M.D. (1990–2003). We have had much in common—long association with, and deep appreciation of and devotion to the Hospital and (after 1963) the Medical School, as well as valued friendships with the many attendings and faculty members who have staffed our institution and its affiliates. From the start, the *Journal* editors have sought to publish some of the important research emanating from Mount Sinai and also the outstanding academic lectures and symposia delivered and conducted here, by leading experts both within and outside the institution. In addition, we have welcomed manuscripts from other institutions and other countries. Since assuming the editorship of the *Journal*, I have attempted to carry on this tradition and, in addition, have encouraged contributions from our younger colleagues, including medical students, house staff and fellowship trainees.

The pages of the *Journal* have included articles on many important advances in medicine over the past 73 years and reflect the remarkable growth of knowledge in medical science and all its specialties during this period. The contributions of Mount Sinai to this growth are well represented. Yet all institutions must change to some extent to remain relevant and important. Beginning with the January 2007 issue, the *Journal* will be published by John Wiley and Sons, Inc. and the new Editor-in-Chief will be Dr. C. Warren Olanow. To them, we offer our fondest wishes for success.

It has been a personal privilege and pleasure to serve as Editor-in-Chief of the *Journal*. In some respects it has been a difficult task, but also a most rewarding one. My deep appreciation and gratitude are expressed to my stalwart assistants, Production Manager, Melva Meyer, and Copy Editor, Ron Stein, for their devoted help and meticulous attention to necessary detail, and to Mr. John Wehle at Tangent Graphics and his assistants, Kathleen Luongo and Steve Daskalakis, for enabling us to publish a journal of high quality. Of course, the *Journal* would not have been possible without the contributions of our many authors and devoted reviewers, to whom we express our sincerest gratitude.

Leslie A. Kuhn, M.D.
Editor-in-Chief

Update On Liver Transplantation:

Indications, Organ Allocation, and Long-Term Care

Patricia M. Lopez, M.D.[1], and Paul Martin, M.D.[2]

Abstract

Liver transplantation (LT) is definitive treatment for patients with acute liver failure and end- stage liver disease and in a subset of primary hepatic malignancies. For patients who successfully undergo LT, the probability of long-term graft and recipient survival is generally excellent, with a high likelihood of return to a relatively normal lifestyle. This article will review current indications, contraindications and postoperative care in LT. With the number of potential recipients far exceeding the number of deceased donor organs, new strategies are being explored to increase access to LT, including: splitting cadaveric donor livers, the use of living donors, and the adoption of the Model for End-Stage Liver Disease (MELD) scoring system, which is based on a mathematical formula to stratify patients in greatest need of transplantation. The allocation of deceased donor organs will, however, remain a contentious issue unless the donor pool is greatly expanded.

Key Words: Liver transplantation.

Introduction

Although the first human liver transplantation (LT) was done in 1963 (1), it has been only in the last two decades that orthotopic liver transplant (OLT) has achieved one-year survival rates of 80–90% (2). According to the United Network for Organ Sharing (UNOS), there are currently more than 17,000 patients on the national waiting list for OLT, but in 2005, only 5,435 liver transplants were performed (3). Thus, many patients die while awaiting organ transplant. This large disparity between the number of available deceased donor organs and qualified recipients awaiting OLT has created an ongoing debate regarding selection criteria, timing of OLT, and attempts to expand the donor pool as mortality for listed patients rises.

There are related issues as well. For example, transplant may not cure the underlying liver disease, and recurrent liver disease after LT remains a major challenge.

Indications and Contraindications

LT is indicated for most causes of acute or chronic liver disease. Cirrhosis accounts for more than 80% of transplants performed in adults, with hepatitis C and alcoholism being the two most common diagnoses (2). Other indications include the cholestatic liver disorders (primary biliary cirrhosis, sclerosing cholangitis, biliary atresia), chronic hepatitis (hepatitis B, autoimmune hepatitis), metabolic diseases (Wilson's disease, nonalcoholic steatohepatitis), fulminant hepatic failure (FHF), and non-metastatic hepatocellular carcinoma (Fig. 1). Major pediatric indications for LT include biliary atresia and metabolic liver disease.

Acceptable tumor dimensions for patients with hepatocellular carcinoma (HCC) under consideration for OLT are either a single lesion less than 5 cm, or if multiple, two or three lesions with the largest not greater than 3 cm in diameter (4). Survival rates for these patients are comparable to those for cirrhosis leading to transplant without a complicating HCC. Preoperative metastatic work-

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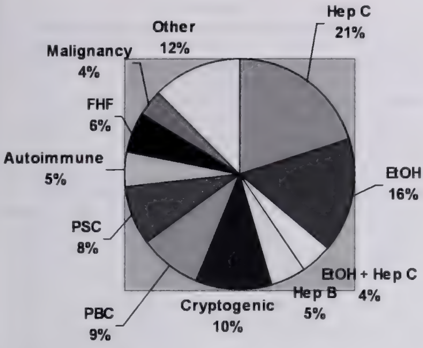

Fig. 1. Indications for liver transplant.

HepC = hepatitis C, PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; EtOH = alcohol; FHF = fulminant hepatic failure.

up includes bone scan, chest CT with an absence of vascular invasion (suggested for instance by an occluded portal vein). Not infrequently, a small "incidental" HCC is discovered in the native liver following OLT. These tumors are typically less than 2 cm in diameter, had not been detected by preoperative imaging, and do not affect survival.

There are relatively few absolute contraindications to OLT. Although organ allocation is centralized, many contraindications to listing for LT are center-specific. In most transplant centers a selection committee composed of hepatologists, transplant surgeons, transplant coordinators, psychiatrists and social workers determines the overall suitability of the transplant candidate. Most generally accepted absolute contraindications to transplantation are noted in Table 1. Centers are now increasingly offering LT to carefully selected older patients and HIV-infected individuals in the absence of AIDS, as part of newer protocols.

Listing and Timing of Transplantation

One of the key issues in LT is appropriate timing of transplant. Any patient with documented FHF is a potential candidate for liver transplantation. The term "fulminant hepatic failure" refers to the rapid development of severe acute liver injury with impaired synthetic function and encephalopathy in a person who previously had a normal liver or had well-compensated liver disease. For FHF, underlying etiology is the single best predictor of outcome without OLT (5). The King's College Criteria are used by many centers to predict outcome of FHF and the need for OLT (Table 2; 5). Early referral of these patients to a transplant center is critical to offer the best chance of survival. Patients with fulminant hepatic failure are given the highest priority on the transplant list (UNOS Status 1).

The presence of cirrhosis alone is not sufficient to warrant transplantation. Although the high level of morbidity and mortality in chronic liver disease is related to complications of cirrhosis, the well-compensated cirrhotic patient can remain stable for many years. Fattovich et al. reported a 91% 5-year survival rate in a cohort of 384 cirrhotic hepatitis C virus (HCV) patients. Predictors of decompensation included age >54, presence of stigmata of chronic liver disease, platelets <130, and bilirubin >17 mmol/L (6). However, once an index manifestation of decompensation had occurred (variceal bleed, ascites, etc.), survival dropped to 50% at 5 years, suggesting that referral for LT should be considered once an index complication has occurred. Although variceal bleeding is the most dramatic and immediately life-threatening presentation of cirrhosis, the onset of ascites or hypoalbuminemia also predicts diminished long-term

TABLE 1

Contraindications to Liver Transplantation

Anatomic abnormality precluding liver transplantation
Malignancy outside the liver
Untreated sepsis
Advanced cardiopulmonary disease
Active alcohol and drug use
AIDS

TABLE 2

Criteria for Liver Transplantation in Fulminant Hepatic Failure (Criteria of King's College, London)

1. Acetaminophen toxicity patients
    A. pH < 7.3 OR
    B. Prothrombin time > 6.5 (INR) and serum creatinine >3.4 mg/dL
2. Other patients
    A. Prothrombin time >6.5 (INR) OR
    B. Any three of the following variables:
        1. Age <10 yrs or >40 yrs
        2. Etiology: non-A, non-B hepatitis; halothane hepatitis; idiosyncratic drug reaction
        3. Duration of jaundice before encephalopathy > 7 days
        4. Prothrombin time > 3.5 (INR)
        5. Serum bilirubin >17.6 mg/dL

Adapted with permission from O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97(2):439–445 (5).

INR = international normalized rate for prothrombin time.

survival. The development of hepatorenal syndrome is an ominous marker that signals the need for immediate transplant evaluation. Thus, the patient with evidence of progression of cirrhosis should be offered the option of referral to a transplant hepatologist for an opinion regarding further management (Table 3; 7).

In addition to referral for LT evaluation, prevention and management of several other complications of cirrhosis need to be considered (Table 4).

The ideal time for LT for chronic liver disease is when the patient has less than 50% chance of surviving 1–2 years but before he or she develops multi-organ complications. Once multi-organ system failure occurs, the survival rate is only 20–30% after transplantation (8). The prognosis of patients with cirrhosis is currently defined using both disease-specific and non-disease-specific clinical tools. The Child-Turcotte-Pugh score has been most frequently used to assess prognosis of cirrhotic patients until recently (Table 5; 9).

Model for End-Stage Liver Disease (MELD) Score

In 1998, the Department of Health and Human Services re-defined policies and principles for organ allocation, to create an equitable system that optimizes potential outcomes for all potential recipients. In 2002, the Organ Procurement and Transplantation Network (OPTN) along with UNOS endorsed the development of a new system based on the Model for End-Stage Liver Disease score for patients who do not have status 1 or are in fulminant liver failure.

TABLE 3

Biochemical and Clinical Indications for Liver Transplantation in Chronic Liver Disease

1. Cholestatic liver disease
    A. Bilirubin >10 mg/dL
    B. Intractable pruritus
    C. Progressive bone disease
    D. Recurrent bacterial cholangitis
2. Hepatocellular liver disease
    A. Serum albumin <3.0 g/dL
    B. Prothrombin time >3 seconds above control
3. Both cholestatic and hepatocellular liver diseases
    A. Recurrent or severe hepatic encephalopathy
    B. Refractory ascites
    C. Spontaneous bacterial peritonitis
    D. Recurrent portal hypertensive bleeding
    E. Severe chronic fatigue and weakness
    F. Progressive malnutrition
    G. Development of hepatorenal syndrome
    H. Detection of small hepatocellular carcinoma

Adapted with permission from Keefe EB. Selection of patients for liver transplantation. In: Maddrey WC, Sorrell MF, editors. Transplantation of the liver. 2nd ed. Norwalk (CT): Appleton & Lange, 1995. pp. 13–60 (7).

TABLE 4

Management of Patients with Compensated Cirrhosis

Endoscopic screening of varices
Prophylaxis of variceal bleeding
Prophylaxis of bacterial peritonitis
Screening and treatment of osteoporosis
Treatment of vitamin deficiencies
Screening of hepatocellular carcinoma
Screening and treatment of diabetes
Vaccinations: hepatitis A, B, influenza, pneumococcus

TABLE 5

Child-Turcotte-Pugh Classification: Class A=5–6; Class B=7–9; Class C=10–15

	1 point	2 points	3 points
Bilirubin (mg/dL)	<2	2–3	>3
Ascites	Absent	Slight	Moderate
Prothrombin time (seconds prolonged)/INR	<4 (INR <1.7)	4–6 (INR 1.7–2.3)	>6 (INR >2.3)
Encephalopathy grade	None	1–2	3–4
Albumin (g/dL)	>3.5	2.8–3.5	<2.8

Adapted with permission from Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG, editor. The liver and portal hypertension. Philadelphia (PA): WB Saunders; 1964; 50:1–85 (9).

INR = international normalized rate for prothrombin time.

The MELD score was originally developed to assess the prognosis of cirrhosis patients undergoing transjugular intrahepatic portosystemic shunt (10), but has been validated in several patient populations to provide a reliable estimate of short-term survival of patients with end-stage liver disease awaiting liver transplantation. The MELD score incorporates values for serum bilirubin, serum creatinine, and international normalized ratio for prothrombin time (INR) in a log-transformed equation to estimate likelihood of 3-month survival. The formula for the MELD score and 3-month mortality is available on the Internet at www.mayo.edu/int-med/gi/model/mayomdl.htm (Table 6; 10).

The potential advantages of the MELD score over the Child-Turcotte-Pugh score are its use of only objective parameters, in contrast to the Child-Turcotte-Pugh score, which incorporates subjective parameters such as the presence of hepatic encephalopathy and ascites. Higher MELD scores have been associated with decreased survival

TABLE 6
Model for End-Stage Liver Disease Score

MELD score	Three-Month Mortality (Hospitalized Patients)
≤ 9	4%
10–19	27%
20–29	76%
30–39	83%
≥ 40	100%

Adapted with permission from Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001; 33(2):464–470 (10).

MELD = $3.8*\log_e$(Bilirubin[mg/dL]) + $11.2*\log_e$(INR) + $9.6*\log_e$(Creatinine[mg/dL]) + 6.4*(Etiology: 0 if Cholestatic or Alcohol, 1 Otherwise)

rates. Three-month survival is less than 20% for patients with a MELD score of 40. The driving force of this system is disease severity, and there is no inherent benefit to early referral. In fact, referral too early may waste time and resources and cause the patient anxiety. A Child-Turcotte-Pugh Score of 7, a MELD score of 10 or any complication of portal hypertension, such as ascites or variceal bleeding, is an appropriate indication for transplant evaluation.

An analysis of the impact on deaths on the waiting list, early patient and graft survival, and waiting list registrations in the MELD era has been recently reported. Freeman et al. noted a 12% reduction in the number of newly listed patients (mainly those with low MELD scores), a 3.5% reduction in deaths while on the waiting list, and unchanged early graft and patient survival as compared to the previous allocation system (11).

The MELD score at which a patient will realistically receive a donor liver varies by region and organ demand. Providers need to know the average MELD score at time of transplant for each blood group in their region, in order to determine the appropriate timing for referral.

Pretransplant Evaluation

The objective of the pretransplant evaluation is to assess whether the patient will be able to tolerate the stress of the surgery, the immunosuppression and the highly demanding post- transplant care, as well as to confirm that the patient requires LT. Each patient undergoes extensive cardiopulmonary and psychosocial evaluation as well as screening for occult infection and neoplasia. Initial assessment should also include a teaching session for the patient and his or her family; this session should include a discussion of the risks and benefits of transplantation, including the potential for poor outcomes and the need to comply with follow-up appointments and medication regimens (12).

Careful psychiatric evaluation must be done on patients with a history of alcohol or drug abuse in order to prevent relapse after transplantation (13, 14). The impact of drug or alcohol use after transplant is still under investigation. However, recidivism has been found for as many as 30% of alcoholics after transplantation and for 20% of patients on a methadone maintenance program (15, 16); recidivism can have an effect on graft function, medical compliance and long-term survival (14).

Advances in Immunosuppression

Post-transplantation immunosuppression consists of “induction” and “maintenance” regimens, as well as treatment protocols for acute cellular rejection (ACR). Acute cellular rejection develops in approximately 70% of liver transplant recipients treated with cyclosporine-based or tacrolimus-based immunosuppression (17). ACR is most frequent 5–14 days following transplantation, but may present later, often in association with inadequate immunosuppression. Early in the post-transplant period, intravenous corticosteroids are used and tapered rapidly over several days with more long-term use of oral steroids. At most centers, maintenance immunosuppression is based on a calcineurin inhibitor (cyclosporine or tacrolimus) started immediately postoperatively with corticosteroids. The induction regimen typically includes high-dose steroids with initial introduction of cyclosporin or tacrolimus. Calcineurin inhibitors bind to intracellular proteins, inhibiting the phosphatase activity of calcineurin, resulting in inhibition of gene transcription for the synthesis of lymphokines such as interleukin (IL)-2. Calcineurin inhibitors have significant side effects including neurotoxicity, nephrotoxicity, hypertension and diabetes (Table 7). Mycophenolate mofetil (an inhibitor of inosine monophosphate dehydrogenase) or azathioprine (an inhibitor of DNA and RNA synthesis) may be used as adjuvant agents in order to allow lower doses of the calcineurin inhibitors in an effort to reduce toxicity. Maintenance immunosuppression in the stable patient generally permits lower therapeutic levels of tacrolimus or cyclosporine. Complete withdrawal of oral corticosteroids within 6–12 months of OLT has become standard in non-autoimmune-mediated liver disease, especially in patients transplanted for chronic viral hepatitis.

TABLE 7
Side Effects of Immunosuppression

Tacrolimus	Cyclosporine	Prednisone
Nephrotoxicity	Nephrotoxicity	Osteoporosis
Tremor	Tremor	Osteonecrosis
Hypertension	Hypertension	Diabetes
Headache	Headache	Hyperlipidemia
Gastrointestinal symptoms	Hirsutism	Hirsutism
Alopecia	Gingival hyperplasia	Hypertension
Diabetes		Cushingoid habitus

Sirolimus (Rapamycin) is a new immunosuppressive agent, which is structurally similar to tacrolimus but acts by inhibiting lymphocyte proliferation. In preliminary studies, it appeared less nephrotoxic than tacrolimus, and when used in combination with tacrolimus or cyclosporine it may allow use of lower levels of the calcineurin inhibitors (18). However, enthusiasm for its use in OLT has been tempered by potentially severe side effects, including delayed wound healing and vascular complications (19). Its role in OLT recipients is still not well defined.

First-line therapy for acute cellular rejection, which is critical in the initial few months after transplant, generally consists of high doses of intravenous corticosteroids tapered over several days (20). Approximately 70–80% of rejection episodes respond to bolus doses of methylprednisolone (21, 22). Acute rejection not responsive to steroids may require addition of other agents, including mycophenolate mofetil, higher levels of tacrolimus, or muromonab-CD3 (OKT3), a monoclonal preparation of antibodies directed against CD3 cells. Chronic rejection typically develops later in the post-OLT course and is characterized by vanishing bile ducts (ductopenia). It may respond to a high dose of tacrolimus but can lead to the need for retransplantation.

Other agents currently undergoing investigation as induction therapy include daclizumab, a humanized monoclonal antibody, basiliximab, a murine-human chimeric antibody, and FTY720, a synthetic analogue of myriocin that inhibits lymphocyte and chemokine actions.

Early Post-transplant Course

Because of the complexity of LT and the often markedly decompensated state of OLT recipients, invasive monitoring in the setting of an intensive care unit is necessary in the first few postoperative days. Markedly abnormal liver biochemistries are typical during the initial 48–72 postoperative hours and reflect a number of insults to the graft, including ischemia following harvesting, preservation, and subsequent reperfusion. However, the overall trend in serum aminotransferase levels should be downward, with a corresponding improvement in coagulopathy and a falling serum bilirubin level. Hepatic artery thrombosis needs to be excluded promptly by Doppler ultrasound and sometimes requires urgent retransplantation. Primary nonfunction of the graft is also an indication for urgent retransplantation.

Within the first week after OLT, liver biochemistries should steadily improve as ischemia and reperfusion damage resolve. Acute cellular rejection becomes an important and frequent cause of graft dysfunction at 1 week and beyond. ACR is suggested by a rise in serum aminotransferase, alkaline phosphatase and bilirubin levels, but the diagnosis requires confirmation by a liver biopsy.

The timing of various infectious complications following liver transplantation is shown in Fig. 2 (23, 24).

Neurologic dysfunction can present in the early-post LT phase, as well as hyperglycemia and renal impairment. They may reflect a number of factors but are mainly related to the toxic effects of cyclosporine and tacrolimus.

After discharge, patients are seen at weekly intervals during the first postoperative month. The liver biochemistries should fall to normal levels within a few weeks following OLT. Any graft dysfunction is an indication for prompt liver biopsy, because ACR remains a concern during this time; in addition, cytomegalovirus (CMV) (25) and early HCV infection recurrence become important considerations three or more weeks after OLT. The guidelines in terms of prophylaxis strategies after LT are shown in Table 8.

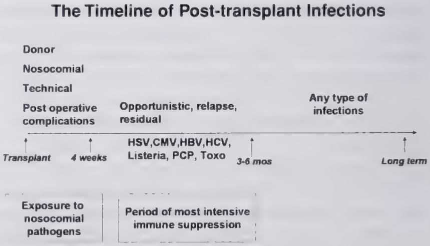
The Timeline of Post-transplant Infections
Donor
Nosocomial
Technical
Post operative complications
Opportunistic, relapse, residual
Any type of infections
HSV,CMV,HBV,HCV, Listeria, PCP, Toxo
Transplant
4 weeks
3-6 mos
Long term
Exposure to nosocomial pathogens
Period of most intensive immune suppression

Fig. 2. The timeline of post-transplant infections.

HSV = herpes simplex virus; CMV = cytomegalovirus; HBV = hepatitis B virus; HCV = hepatitis C virus; PCP = pneumocystis carinii pneumonia; Toxo = toxoplasmosis.

TABLE 8
Infectious Diseases Guidelines

	Prophylaxis Strategy
Antibacterial	
Without significant infection history	ampicillin/sulbactam (before LT and for 48 hours after LT)
History of significant infection	vancomycin (before LT and for 48 hours after LT)
Antifungal	
In high-risk patients (re-transplants, FHF, renal failure, prolonged surgery)	IV fluconazole × 7 days followed by PO clotrimazole × 1 month
Low-risk patients	PO clotrimazole troche × 1 month
PCP	PO trimethoprim / sulfamethoxazole (TMP/SMX) × 3 months or atovaquone or pentamidine in allergics or intolerants to TMP/SMX
CMV	
CMV recipient + /donor + or -	PO valganciclovir 450 mg/d × 3 months
CMV recipient - / donor +	PO valganciclovir 900 mg/d × 3 months
CMV recipient -/ donor -	PO valacyclovir 500 mg/d × 3 months

LT = lung transplantation, PCP = pneumocystis carinii pneumonia, FHF = fulminant hepatic failure, TMP = trimethoprim, SMX = sulfamethoxazole, CMV = cytomegalovirus.

Fungal infections pose a major threat to the LT recipient, particularly in the setting of marked debilitation, intensive immunosuppression for rejection, or retransplantation. Major sites of infection are mucocutaneous (oral and esophageal), pulmonary, and intracerebral. Despite prolonged therapy with amphotericin or more recently with itraconazole, a fatal outcome is usual.

Long-Term Primary Care Management Issues

As the number of LT recipients continues to increase, and the five-year survival rate exceeds 70%, the non-transplant physician is playing a larger role in the care of these patients. Along with general preventative medicine, primary care management issues specifically related to immunosuppressive therapy include obesity, hyperlipidemia, hypertension, diabetes, osteoporosis, and screening for malignancy.

Routine health maintenance, as recommended by the US Preventive Services Task Force (26), should be applied to post-LT patients. This includes annual physical exams and age—appropriate screening for cholesterol, hypertension, breast cancer, colon cancer, cervical cancer, skin cancer and diabetes.

Patients frequently experience weight gain and obesity after LT (27). Body weight tends to increase during the two years after transplantation, before stabilizing. Excessive weight gain is frequent and 20–40% of patients become obese (body weight >30 kg/m^2). Reasons for weight gain include use of prednisone, appetite stimulation by the anti-rejection regimens and an increased sense of well being after long-term chronic illness, often with a lack of pre-LT dietary restriction. Appropriate dietary counseling and an exercise program should be initiated.

Hyperlipidemia, with a mixed profile of elevated cholesterol and triglyceride levels, is noted in up to 30% of OLT recipients (28). Elevated lipid levels may be associated with allograft vasculopathy. The etiology of hyperlipidemia is multifactorial, including obesity, medications (cyclosporine inhibition of bile acid synthesis, influence of sirolimus), and pre-transplant-related risk factors. Treatment of obesity and diabetes as well as dietary and lifestyle modification are the first-line measures. For many patients, hyperlipidemia improves over time if the maintenance doses of steroids and cyclosporine are at low levels (29). Thus, medical treatment is rarely indicated early in the course when steroid doses are relatively high. If serum lipids do not fall, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors can be safely prescribed (30). Myositis, rhabdomyolysis and hepatotoxicity are uncommon side effects. Choice of agent is dependent on cost and degree of hyperlipidemia. Nicotinic acid can decrease glucose tolerance and raise uric acid levels, leading to symptomatic gout in some patients. Bile-acid binders lower cholesterol but tend to raise triglyceride levels and impair the absorption of cyclosporine. Gemfibrozil may be considered for the treatment of refractory hypertriglyceridemia. However, its combination with a statin is contraindicated due to an increased risk of rhabdomyolysis.

Systemic hypertension develops in 55–85% of patients within the first year after LT (31). Hypertension is multifactorial but can be attributed partly to the immunosuppressive regimen, especially the calcineurin inhibitors and steroids (32, 33). The prevalence of hypertension increases with length of time from transplant. Initial treatments of hypertension include dietary sodium restriction and, if possible, dose reduction of calcineurin inhibitors and prednisone. In a majority of cases, antihypertensive medication is required, and calcium channel blockers have proven effective, without significant nephrotoxicity. Diltiazem and verapamil may elevate cyclosporine and tacrolimus levels. If blood pressure control is not adequate with a calcium channel blocker, a beta-blocker such as labetalol, diuretics, and angiotensin-converting enzyme inhibitors (such as enalapril and captopril) or angiotensin II receptor antagonist may be required.

Impaired glucose tolerance and diabetes are common in cirrhotic patients due to peripheral insulin resistance, which predisposes them to post-transplant diabetes. The diabetogenic potential of immunosuppressives, mainly tacrolimus, cyclosporine and corticosteroids, as well as weight gain, are important exacerbating factors (34). For unclear reasons, the risk also appears to be increased in patients transplanted for hepatitis C (35). Patients who are diabetic prior to transplantation typically require insulin after the transplant, and 13–30% of patients develop *de novo* diabetes. The incidence of *de novo* diabetes is higher with tacrolimus than cyclosporine. Treatment of diabetes in post-OLT patients is based on the same principles on which treatment of the nontransplant patient is based. Diet, lifestyle modification, weight loss, and the addition of insulin or oral hypoglycemic agents may be indicated, glyburide being an initial choice. Metformin is best avoided. Side effects of the oral hypoglycemics should be monitored, including hepatotoxicity. Calcineurin inhibitor dose reduction and steroid withdrawal can be considered by the transplant team (29, 34).

Osteopenia is common in cirrhotic patients and typically is due to osteoporosis rather than osteomalacia, although the latter can occur in severely cholestatic patients. Bone disease occurs after liver transplantation (36). Factors implicated, apart from calcium and vitamin D deficiency, include low muscle mass, immobility, long-term corticosteroid use, poor nutrition, and alcohol abuse. After transplantation, rapid bone loss occurs in the first 3–6 months, but bone density increases to pretransplant levels by 6–12 months, and may show a trend toward further improvement thereafter (37). The rapid bone loss occurring in the first three months is primarily due to the high doses of corticosteroids used immediately after transplantation (38). The most important risk factor for symptomatic post-transplant bone disease is a low bone mass prior transplant. For patients awaiting LT, serum calcium, phosphorus, thyroid function studies, and parathyroid hormone should be evaluated along with bone densitometry studies. In addition to calcium and vitamin D, calcitonin or bisphosphonates may be considered as supplements if bone density indicates osteoporosis or if long-term corticosteroids are used. Once-weekly oral dosing with alendronate or risedronate is well tolerated and convenient (39). Mobilizing patients soon after surgery can help curb bone loss in the immediate post-transplant period.

As with other solid transplants, the incidence of malignancy is increased for liver transplant patients (40). Skin cancer, lymphoma, primarily non-Hodgkin's, and oropharyngeal cancers may be more common in the post-LT population. The overall incidence of post-transplant lymphoproliferative disease is 30–50 times higher than that in the general population (41). The risk is greatest in patients with high degrees of immunosuppression. Epstein-Barr virus infection is thought to be responsible for most post-transplant lymphomas (42). The underlying liver disease also may predispose patients to develop specific types of cancer after liver transplantation. Patients transplanted for primary sclerosing cholangitis who have inflammatory bowel disease remain at high risk for colonic dysplasia and colon cancer (43). The primary care physician and gastroenterologist, along with the transplant team, should perform routine examination and screening.

Recipients beyond 6 months after OLT should be vaccinated for influenza, pneumococcus, and tetanus. Live vaccines for illnesses such as measles, mumps, rubella, and live oral polio vaccine should not be given.

Recurrent Disease after Transplantation

With improved long-term post-OLT survival, disease recurrence has become more evident. In the early 1990s hepatitis B recurrence was observed in more than 80% of LT recipients, and accounted for 73% of all deaths of patients transplanted for this indication (44). Currently, effective antiviral prophylaxis with high-dose hepatitis B immunoglobulin (HBIG) (more recently combined with lamivudine and adefovir) has virtually eliminated HBV recurrence (45, 46). The overall survival of patients transplanted for HBV-related cirrhosis currently exceeds 80% at one year and 65% at three years (47). The major challenge now in managing HBV-infected patients perioperatively is to provide adequate immunoprophylaxis in a cost-effective manner, given the high cost of long-term HBIG use, especially when given intravenously. To reduce the costs of HBIG therapy, attempts have been made to substitute maintenance IV HBIG with IM administration. Combination therapy with HBIG and antiviral treatments can reduce reinfection rates to 10% with low doses of IM HBIG (48). Although reinfection rates have been dramatically reduced with HBIG prophylaxis and lamivudine, other issues, including viral resistance and optimal duration of therapy with HBIG, have yet to be resolved.

Cirrhosis due to hepatitis C virus is the most common indication for OLT in the United States. After transplantation, hepatitis C recurrence is nearly universal, with histological changes in 50–80% of patients (49). Virologic reinfection at the time of transplantation is not surprising, since almost all patients with HCV undergoing transplantation are viremic (50). Furthermore, peripheral monocytes harbor HCV and may act as a source of virus, which reinfects the donor liver (51). The outcome of patients transplanted for HCV is variable. Recent analysis of the UNOS database showed diminished survival rates for HCV-positive patients compared to HCV-negative transplant recipients at 5 years (65.6% vs. 56.7%) (52). Evidence is accumulating that the post-transplant course of HCV infection is accelerated compared to the pretransplant setting. A report from King's College found that protocol biopsies done 5 years after transplant showed that 20% of patients transplanted for HCV already had evidence of allograft cirrhosis (53, 54). There is no consensus on the role of prophylactic antiviral therapy to prevent HCV recurrence after OLT (55). A recent study using combination ribavirin and pegylated interferon for managing recurrent HCV is promising (56). However, there is no consensus on the optimal strategies for administering therapy. Because of the side-effect profile of these drugs, many patients are not eligible for treatment or they withdraw during therapy. Most transplant centers attempt to reduce immunosuppression and treat rejection cautiously. Until more is known about host and viral factors that may predispose transplant patients to aggressive recurrent disease, the treatment and timing of the initiation of therapy remain undefined.

HCV recurrence may ultimately lead to the need for retransplantation. Unfortunately, the prognosis for such patients is generally poor (57–61).

Recurrence of hepatocellular carcinoma (HCC) can be minimized by exclusion of high-risk candidates with features predictive of tumor recurrence: tumor size and number and evidence of vascular invasion (62). Based on a large European experience reported by Mazzaferro and colleagues, generally accepted criteria for OLT in patients with HCC have included a tumor diameter of less than 5 cm if the tumor is solitary or, if multiple, two or three lesions with the diameter of the largest lesion being no greater than 3 cm (4). Survival rates comparable to those for transplantation for decompensated cirrhosis in the absence of complicating HCC (75% at 4 years) have been reported. Cholangiocarcinoma has historically been a contraindication to transplant due to rapid tumor recurrence. Recent protocols with adjuvant external beam radiation and chemotherapy have shown early promise and may permit carefully selected patients with primary sclerosing cholangitis (PSC) and cholangiocarcinoma to be transplanted (63).

Graft failure secondary to recurrence of PSC, primary biliary cirrhosis (PBC), and autoimmune hepatitis has been observed in a subset of patients, although less frequently or rapidly than for viral hepatitis. A report from the Mayo Clinic described PSC recurrence in 20% of OLT recipients using cholangiographic and hepatic histologic criteria. For a majority of individuals recurrent disease was mild, but 8% required retransplantation (64). It is now generally accepted that PBC can recur following LT, although there was much initial debate. A precise estimate of the recurrence rate is uncertain, since not all studies have used uniform criteria for defining recurrent PBC, and studies have had variable follow-up. In a series of 400 patients from Birmingham, England, recurrence was observed in 18% at five years and 30% at 10 years (65). Recurrent autoimmune hepatitis, as defined by histologic chronic hepatitis, positive autoantibodies >1:40 and the need for steroid increase, was noted in 13/47 patients in one series (66). Risk of recurrence increased with prednisone withdrawal or lower immunosuppression. Hence, individuals transplanted for autoimmune liver disease may not tolerate complete prednisone withdrawal.

Retransplantation for recurrent disease is a difficult ethical issue faced by transplant teams in an era of intractable organ shortage. Perioperative risk, survival, quality of life, as well as the presence of comorbidities such as renal failure related to immunosuppression toxicity all need to be weighed in the decision to retransplant.

Novel Strategies

In order to maximize donor organ access for adult and pediatric recipients, novel surgical and liver replacement procedures have evolved. Newer surgical techniques include split cadaveric liver and living donor transplantation (67).

Cadaveric split liver transplantation creates two functioning allografts: the left lateral segment for a child and a right trisegment for an adult. The advantage of split liver transplantation is that it increases the total number of transplants performed from a static cadaveric donor organ supply. Disadvantages include greater technical complexity, longer procurement times, and feasibility only in a subset of donor organs.

Live donor liver transplantation (LDLT) provides one means to expand organ availability (68). Ethical concerns regarding LDLT are related to the potential for donor morbidity and mortality (68, 69). Opponents argue that it is unacceptable to place a healthy donor at risk of long-term debility or death. Despite these risks, proponents of LDLT suggest that it is unethical to deny an informed and willing adult the opportunity to participate in the donation process.

LDLT was initially performed for pediatric recipients. Access to LDLT had a dramatic impact on reducing mortality on the pediatric waiting list, with excellent recipient and graft survival rates reported. LDLT in adults is an even more technically challenging endeavor (70). A potential live donor is extensively evaluated for candidacy, as is shown in Table 9 (71). Every effort should be made to confirm that consent is informed and to ensure that the prospective donor has adequate time to contemplate the risks of the procedure and to decline participation, if desired. Advantages of living donor transplantation include expansion of the donor pool, ability to assess graft quality prior to transplant, and elective transplantation before significant debilitation of the potential recipient. Disadvantages are that living donor transplants require greater surgical technical skill and that donor morbidity and mortality from major abdominal surgery can occur. Donor morbidity is estimated at 10–20%, with major complications being biliary leaks, gastrointestinal complications, and vascular injury. Donor mortality is estimated at 0.2–1% (72, 73).

Conclusion

Liver transplantation has revolutionized the management of acute and chronic liver diseases. The scarcity of donor organs is still the factor limiting its use. In parallel to the evolution of liver transplantation, the care of both transplant candidates with severe liver disease and post-OLT patients has become a major clinical challenge, with the transplant team combining the skills necessary to practice multidisciplinary medicine.

TABLE 9

Evaluation of Prospective Living Liver Donors

Blood group compatibility
Comprehensive history and physical examination
Routine laboratory studies including viral serologies, HIV
Anatomic imaging: liver volume, vascular anatomy, biliary anatomy
Pulmonary function tests
Cardiac clearance
Psychosocial evaluation: life circumstances, motivation, understanding
Independent advocate opinion
Review of candidacy with prospective donor
Presentation to selection committee

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Translational Research in Inflammatory Bowel Disease

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Abstract

The idiopathic inflammatory bowel diseases (IBDs), broadly classified as either Crohn's disease (CD) or ulcerative colitis (UC), are caused by a dysregulated mucosal immune response to a luminal antigen, possibly a bacterium, in a genetically predisposed host. A rapid expansion of knowledge in recent years has greatly increased our understanding of the pathophysiology of these disorders. For example, the relatively recent discovery of the NOD2 gene, a protein involved in bacterial sensing, has provided further evidence of the complex interplay between hosts and microbes in Crohn's disease. Significant recent advances have also occurred with the discovery of the role of Toll-like receptors and dendritic cells in the development of gut inflammation, and the role of proinflammatory cytokines in the development and potentiation of gut inflammation. This article presents an update on these key developments and emphasizes the translational aspects of research that are directly related to patient care.

Key Words: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, innate immunity, adaptive immunity, biological therapies.

Introduction

THE IDIOPATHIC INFLAMMATORY bowel diseases can be broadly classified into either Crohn's disease or ulcerative colitis. Crohn's disease can affect any part of the gastrointestinal tract and is characterized by patchy, transmural, potentially granulomatous inflammation, while ulcerative colitis is manifested as diffuse mucosal inflammation that extends proximally from the rectum, which is always involved. Recent research, however, suggests that a spectrum of disorders is present, comprising variant subtypes of inflammatory bowel diseases. It is now understood that no single cause is responsible for the activation of intestinal inflammation in IBD. Instead, IBD is believed to result from an altered gut immune response to a luminal antigen, possibly a bacterium, in a genetically susceptible host (Fig. 1). The hallmark of IBD is intestinal inflammation that leads to disruption of the gut's protective barrier function and direct exposure of luminal bacteria to the mucosal immune system. In a patient with non-diseased gut, inflammation is tolerated and controlled, while in a patient with IBD there is a dysfunction of one or more critical elements responsible for downregulation of inflammation, and a cycle of ongoing, active inflammation occurs.

Genetic Predisposition

Approximately 10–15% of IBD cases are familial, with familial clustering of CD and UC families occurring such that 75% of families are concordant for disease type, and 25% have both CD and UC within the same family (1). Monozygotic twin concordance rates provide estimates of penetrance and are higher in CD (42–58%) than in UC (6–17%). The complementary strategies of genome-wide linkage scanning and candidate gene

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Glossary

ASCA = anti-*saccharomyces cerevisiae* antibody
CARD 15 = c-terminal caspase recruitment domain 15
CBir1 = anti-flagellin antibody
CD = Crohn's disease
CDP 870 = certolizumab pegol
Fc = F constant domain
IBD = inflammatory bowel disease
ICAM-1 = intercellular adhesion molecule-1
IFN = interferon
IL = interleukin
JC = human polyomavirus JC virus
LRR = leucine-rich repeat
MAdCAM-1 = mucosal addressin cell adhesion molecule-1
MAPK = mitogen-activated protein kinase
MDP = muramyl dipeptide
NFκB = nuclear factor kappa B
NOD2 = nucleotide-binding oligomerization domain 2
OCTN = organic cation transporter
OmpC = outer membrane porin of *E. Coli*
pANCA = perinuclear anti-neutrophil cytoplasmic antibodies
PAMP = pathogen-associated molecular pattern
PML = progressive multifocal leukoencephalopathy
TGF = transforming growth factor
Th1 = T-helper 1
TLR = Toll-like receptor
TNF = tumor necrosis factor
Tr1 = T regulatory 1
UC = ulcerative colitis
VCAM = vascular cell adhesion molecule-1

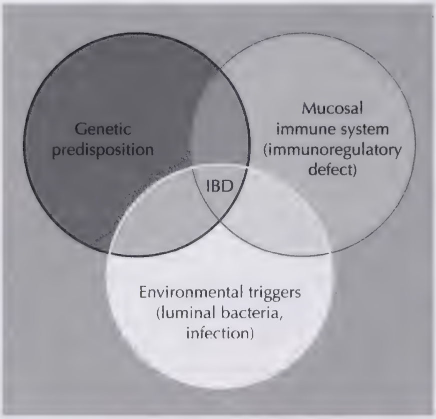
Genetic predisposition
Mucosal immune system (immunoregulatory defect)
IBD
Environmental triggers (luminal bacteria, infection)

Fig. 1. Pathogenesis of inflammatory bowel disease. The interplay of genes and the environment culminates in chronic intestinal inflammation.

analysis have identified two genes associated with susceptibility to IBD at loci IBD1 (chromosome 16) and IBD5 (chromosome 5). The first gene, identified in 2001 on chromosome 16, was the nucleotide-binding oligomerization domain 2 (NOD2) gene, subsequently renamed c-terminal caspase recruitment domain 15 (CARD15). This gene is found in macrophages, dendritic cells, intestinal epithelial cells and Paneth cells, and encodes a protein that plays an important role in antigen recognition and nuclear factor kappa B (NFκB) release with subsequent transcription of proinflammatory cytokines. The three most common mutations of NOD2/CARD15 involve alterations in or near the gene's leucine-rich repeat (LRR) region, which is responsible for the recognition of bacterial antigens. Carriage of NOD2/CARD15 allelic variants is present, however, in only 27–39% of patients with CD, 12–14% of patients with UC and 14–16% of normal controls (2). In cell lines expressing NOD2, activation of mutant NOD 2 by bacterial muramyl dipeptide (MDP) leads to increased production of NFκB and other proinflammatory cytokines (3). Clinically, mutations in NOD2 have been associated with fibrostenosing disease, younger age of onset of disease, ileal disease location and a history of surgery (4).

More recently, a second Crohn's disease susceptibility gene was found on chromosome 5; the proteins encoded by this gene are two organic cation transporters (OCTN 1 and OCTN 2) believed to be responsible for transport of carnitine and other substances across cell membranes. Mutations in one of the two proteins were found in 53% of patients with CD and 23% of healthy controls (5). Mutations may cause disease by reducing carnitine transport in epithelial cells, thereby disrupting β-oxidation, or they may lead to increased transport of harmful bacterial antigens, thereby potentiating upregulation of the mucosal immune response.

Epithelium, T cells and Cytokines

Unlike mucosal defense systems in other organs, which operate under sterile conditions, the gut epithelium and its immune system have developed mechanisms to protect against the chronic inflammation induced by continuous exposure to luminal microbes. The epithelium provides the first relatively impermeable barrier to luminal contents, but luminal bacteria are sampled continuously by M cells and dendritic cells, and transported to lymphoid follicles or Peyer's patches, where they are presented to naïve T cells. These T cells then produce anti-inflammatory cytokines such as transforming growth factor (TGF)-β and interleukin (IL)-10, which help regulate a continuous low-grade inflammation. Although this model is relatively well worked out for the small intestine, the sampling of luminal contents in the colon is less clear. Multiple levels of evidence support the hypothesis of "no bacteria—no colitis," including epidemiological evidence, serum immune reactivity to microbial antigens, identification of specific bacteria more prevalent in IBD patients (e.g., *Pseudomonas fluorescens*, adherent *Escherichia coli*), an increase in adherent bacteria in IBD patients, and clinical improvement with antibiotics and probiotics (4). Serological antibody markers to microbial components may yield important clues to the underlying microbial immunopathology of specific clinical phenotypes in the future, and are most helpful in CD. Antibodies to the yeast cell wall of *Saccharomyces cerevisiae* (ASCA; Anti-*saccharomyces cerevisiae* antibodies) are present in 55–65% of CD patients, and antibodies to the outer membrane porin of *E. coli* (OmpC) are found in 38–50% of CD patients. Anti-I2 antibodies (to a bacterial sequence in *P. fluorescens*) are present in 54% of CD patients, and recently antibodies to an enteric bacterial flagellin, CBir 1, were described in 50% of a CD cohort (6). By contrast, in ulcerative colitis, perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) are present in 50–65% of patients. Clinical data suggest that expressing multiple antibodies at high levels (as in approximately 25% of the CD population) increases the risk of disease progression from inflammatory to fibrostenotic or perforating complications, and that these patients may benefit from more aggressive medical treatment earlier in the course of disease (7).

Below the epithelial layer the mucosal immune system activates various signals that lead to production of pro- and anti-inflammatory cytokines. Undifferentiated T cells are guided to become either T helper 1 or T helper 2 effector cells (Th1 or Th2) or regulatory T cells (Th3 and Tr1) in response to antigenic stimulation. Experimentally, inflammation can be explained by an imbalance between effector cells and regulatory cells. An excess of effector T cells leads to overproduction of proinflammatory cytokines, whereas an excess of regulatory T cells leads to immune tolerance and anergy. Another dimension of epithelial barrier function relates to colonic epithelial cell mucus production, which is reduced in IBD patients and contributes to the hyperresponsiveness of the mucosal immune system to bacteria (8). Classically, CD has a Th1-type cytokine profile, driven by exposure to IL-12, IL-18 or IL-23 and producing IL-2 and interferon (IFN)-γ, which then activate macrophages and the release of IL-1, IL-6 and tumor necrosis factor (TNF)-α. In contrast, UC has a Th2-type cytokine profile characterized by production of IL-4, IL-5, and IL-10 (4), after the activation of natural killer T cells. In reality the distinction between Th1 and Th2 immunophenotypes for each disease is probably less distinct, and it is now recognized that significant overlap exists in the immune responses of the two disorders.

Additional cytokines more recently recognized as being important in the pathogenesis of IBD are IL-17, IL-12 and IL-23. IL-17 is produced predominantly by a specific, newly recognized subset of T cells known as T_{IL-17} cells, but also by monocytes and macrophages. IL-17 is a potent pro-inflammatory cytokine, elevated in both serum and inflamed mucosa of active Crohn's disease and ulcerative colitis patients, especially the former. In contrast, IL-17 levels are not elevated in normal colonic mucosa or the mucosa of patients with active ischemia of infectious colitis. IL-17 activates the NFκB and mitogen-activated protein kinase (MAPK) pathways and induces the synthesis of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8 and TNF-α, increases surface expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and up-regulates the production of nitric oxide. Elevated levels of IL-17 have been found in several chronic inflammatory disorders, including IBD, rheumatoid arthritis, multiple sclerosis, and bronchial asthma. In IBD, serum and mucosal IL-17 levels appear to correlate with disease activity (9). Murine models using IL-10-deficient mice that develop spontaneous enterocolitis have demonstrated the attenuation of intestinal inflammation with anti-IL-17 monoclonal antibodies (10), thereby making IL-17 a potentially attractive therapeutic target in IBD.

Interleukins 12 and 23 are two similarly structured heterodimeric pro-inflammatory cytokines that share a common p40 subunit and act through a common β1 receptor. Interleukin-12 and IL-23 are believed to activate specific subsets of T cells to produce Th1 responses, with IL-23 influencing to the production of IL-17 and IL-6, thereby demonstrating its importance in initiating and perpetuating the chronic intestinal inflammation of IBD (11). Anti-p40 monoclonal antibodies against IL-12 and IL-23 have been shown to ameliorate intestinal inflammation in IL-10-deficient murine colitis models (12), and more recently anti-IL 12 antibodies have been shown to be successful in inducing response and remission in humans with Crohn's disease (13). The centrality of IL-23 to the pathogenesis of T-cell mediated colitis makes it another potential therapeutic target in the treatment of these diseases in humans. Since IL-23 is composed of p40 and p19 subunits, antibodies against p19 would selectively inhibit IL-23 while not affecting IL-12.

After the release of potent cytokines such as TNF-α or IL-1β, and the activation of NFκB pathways, further recruitment of inflammatory cells to the intestinal mucosa occurs through upregulation of adhesion molecules such as mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Cytokines upregulate expression of adhesion molecules on the vascular endothelium in the gut and influence recruitment of inflammatory cells from the bloodstream to the intestinal mucosa via the interaction of adhesion molecules with leukocyte cell surface markers α4β7 and α4β1 (Fig. 2) (14). Strategies that block either the leukocyte surface marker or the adhesion molecule on the endothelial surface can inhibit recruitment of lymphocytes and monocytes to the intestinal mucosa. Another way in which immune cells exit from the circulation is through the action of chemokines. Intestinal epithelial cells produce CCL25, which is chemoattractive to CCR9-expressing lymphocytes. In animal models, CCR9 antagonists inhibit both small bowel and colonic inflammation. Phase 1 and 2 studies with a CCR9 small molecule inhibitor are ongoing in humans.

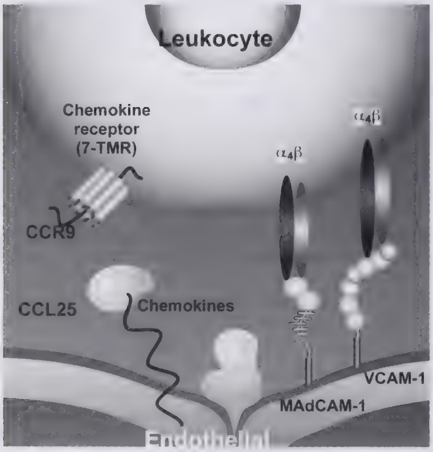

Fig. 2. Adhesion molecule and chemokine expression in the intestine. Leukocytes expressing apha4beta7 or alpha4beta1 bind the endothelial adhesion molecules MAdCAM-1 and VCAM-1. Intestinal epithelial cells secrete CCL25, which chemoattracts leukocytes expressing CCR9. This interaction leads to integrin activation, firm adhesion, and ultimately diapedesis out of the vasculature and into the lamina propria.

7-TMR = seven-transmembrane receptor

Innate and Adaptive Immunity

Broadly speaking, immunity can be classified as adaptive or innate (Fig. 3; 15). Adaptive immunity is mediated by T and B lymphocytes that proliferate clonally in response to a specific antigen, with this response requiring a couple of days through the generation of memory T and B lymphocytes. In contrast, the innate immune system provides immunity in the first minutes to hours after infection. The understanding of innate immunity was dramatically increased in the 1990s with the discovery of the Toll-like receptor (TLR) group of proteins. Ten TLRs have been described; these surface receptors help protect the host from pathogens by the recognition of microbial ligands such as pathogen-associated molecular patterns (PAMPs) which are shared by many luminal pathogens (16). In the gut, TLRs are located on epithelial cells, endothelial cells, dendritic cells, macrophages, and other immune cells. Expression of TLRs, especially TLR4 and TLR2, is increased on the intestinal macrophages and intestinal epithelial cells of patients with IBD. Also, evidence

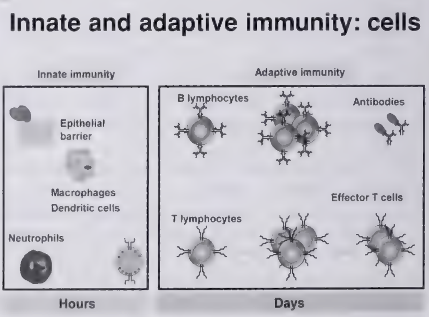

Fig. 3. The innate and adaptive immune responses to exogenous antigen exposure.

Adapted with permission from Abbas A, Lichtman A, Pober J. Cellular and molecular immunology 4th ed. W.B. Saunders; 2000. Fig. 1.1. p. 4. (15).

from IBD animal models suggests that the absence of TLR4 expression protects against Th1-mediated colitis (17), providing further evidence that altered TLR expression plays a role in the pathogenesis of intestinal inflammation. TLR activation leads to downstream events that culminate in the nuclear translocation of NFκB, with the subsequent production of pro-inflammatory cytokines and therefore Th-specific responses.

Intestinal dendritic cells act as a bridge between the innate and adaptive immune systems and are responsible for determining whether immune tolerance or activation occurs, and if it is activation, whether a Th1 or Th2 response predominates. Intestinal dendritic cells are antigen-presenting cells that are found beneath the epithelium in the lamina propria, Peyer's patches and mesenteric lymph nodes. Dendritic cells sample luminal contents directly by extending projections through to the intestinal lumen between epithelial cells, or indirectly via M cells, which are specialized epithelial cells that transport luminal antigens to intestinal lymphoid follicles and Peyer's patches. Upon sampling luminal contents through their surface TLRs, dendritic cells then express potent cytokines of either the Th1 or Th2 variety. Dendritic cells exhibit mobility in response to different stimuli and are able to migrate from peripheral blood to gut mucosa to Peyer's patches and mesenteric lymph nodes in response to particular antigens. Dendritic cells also stimulate intestinal T cells and can influence lymphocytic migration to the gut through the upregulation of homing proteins such as CCR9 and integrin α4β7 (18). Additionally, in IBD, dendritic cells may play a role in disease pathogenesis. In inflamed CD mucosa, specific subsets of dendritic cells secrete very high levels of TNF-α and low levels of the anti-inflammatory cytokine IL-10 in response to antigenic stimulation by lipopolysaccharide (19). Whether therapeutic manipulation of these dendritic cell subpopulations may be beneficial in IBD remains to be determined.

Targeting Therapy to Pathogenesis

Our current picture of the mucosal immune system suggests that treating IBD requires restoring the intricate balance of competing cytokines and/or the cells that produce them. Methods to counter the dysregulated intestinal inflammation in IBD include blocking downstream effectors like cytokines, inhibiting T-cell activation itself by blocking surface costimulatory molecules, and inhibiting leukocytic migration and uptake into the intestinal mucosa. The first phase of biological therapies has used monoclonal antibodies to antagonize a variety of Th1 cytokines, with the anti-TNFα monoclonal antibody infliximab being the prototype agent utilized successfully initially in CD (20 –22). More recently, infliximab has been shown to be almost as efficacious for the induction and maintenance of remission in ulcerative colitis (23), again demonstrating the significant overlap that occurs between Th1 and Th2 cytokines in the two conditions. Subsequently, alternative successful anti-TNFα strategies in CD employed agents with different pharmacokinetic properties, including larger pegylated molecules such as certolizumab pegol (CDP 870) (24) utilized to increase drug half-life and duration of response, and agents given via alternate routes such as the subcutaneous adalimumab (25–27). However, neither of these agents is presently commercially available. Following the success of infliximab, investigators sought to antagonize alternate pro-inflammatory Th1 cytokines in Crohn's disease, and demonstrated efficacy and safety with monoclonal antibodies directed against interferon gamma (fontolizumab) (28) and IL-12 (13). Again, however, the use of these agents remains experimental at present.

In addition to antagonizing individual cytokines, blocking T cell activation is another strategy employed more recently in IBD clinical trials. Visilizumab is a humanized, constant domain (non-Fc) receptor binding anti-CD3 monoclonal antibody that binds to the CD3 component of the T cell receptor complex and induces apoptosis of activated but not resting T cells. Having demonstrated success in the treatment of post-transplant acute graft-versus-host disease (29), visilizumab is currently being tested in severe, steroid-refractory ulcerative colitis as an alternative to colectomy. Initial results are encouraging, although longer-term data are needed before the role of this agent for this indication is clearly known.

An alternative biological strategy is the use of anti-adhesion monoclonal antibodies that can block the uptake of lymphocytes to the lamina propria of the intestine, given that lymphocytes migrating to the intestine commonly express the cell surface marker α4 integrin, usually in combination with β1 or β7. Such anti-adhesion molecules include natalizumab (anti-α4 integrin), which has demonstrated efficacy in CD (30, 31), and MLN-02 (anti-α4β7 integrin), which has achieved modest success in UC (32). However, significant safety concerns have recently arisen about natalizumab, with the discovery of several cases of human polyomavirus JC-virus-associated progressive multifocal leukoencephalopathy (PML) in patients treated with the drug for Crohn's disease and multiple sclerosis (33). As a result, clinical trials using this agent have been discontinued until its safety can be ascertained.

In addition to immune modulation with biological therapies, treatment of IBD aims to restore the delicate host-microbial relationship; antibiotics and probiotics are used for this purpose. The antibiotics metronidazole and/or ciprofloxacin can treat Crohn's colitis and ileocolitis (34–36), perianal fistulae (37) and pouchitis (38), but not ulcerative colitis (39) (ideally, patients with "bacterially sensitive" disease would be identified by phenotypic markers as a way to increase the response rate to these agents). Repopulation of the intestinal lumen with probiotics, or so-called "good bacteria," is a widely pursued strategy with IBD, to an extent that is greater than the clinical trial evidence to support their use. Probiotics increase barrier function, protect against *Salmonella* species infections (40), increase secretion of IL-10 (41) and reduce plasma cell responses to commensal bacteria (42); they are thought to act at least partly via TLR9 signaling. Randomized, controlled trials support the use of probiotics for the prevention of acute pouchitis (43) and the treatment of chronic and refractory pouchitis (44, 45), but results are mixed for the primary treatment of CD (46, 47) and UC (48).

Newer Technologies

Most of the research covered here has focused on the alterations in mucosal immunology that contribute to IBD, but newer approaches to elucidating the pathogenesis of the disease are appearing. They involve new technologies such as microchip array technology and mass spectrometry to identify genes or proteins expressed in the mucosa of IBD patients. The "IBD chip" of a panel of genes known to be associated with IBD may in the future provide a genetic means of predicting disease outcomes from the time of diagnosis. These developments may also make possible the creation of specific small molecules or monoclonal antibodies to antagonize the function of these specific proteins. Future therapies for IBD may well include a combination of agents that manipulate the microbial environment and agents that aim to reset the immunological thermostat. These therapies will be targeted to match the specific pathogenetic phenotype of disease in individual patients. Individual disease phenotypes will be ascertained by a combination of clinical, radiological and endoscopic means, as is currently done, but also genetic and detailed serological profiles will be obtained, with future techniques perhaps including the assessment of individual cytokine profiles for each patient, enabling a more accurate assessment of disease prognosis and the use of specific therapies to antagonize specific inflammatory mediators.

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Acute Ischemia of the Lower Extremity in the Pediatric Population:

A Protocol for Management

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Abstract

Each year, a large number of infants and children undergo vascular catheterization via access in a lower extremity. The femoral system is relatively easy to cannulate, and this approach avoids use of more central access approaches that may present more serious complications. Infrequently, however, pediatric patients develop acute ischemia of the ipsilateral lower extremity. Several surgical and nonsurgical treatment options exist for the management of such problems. However, no adequate protocol exists for the management of acute lower extremity ischemia in the pediatric population. The authors present several cases of distal lower extremity ischemia as a result of femoral artery catheterization and offer a protocol for management of similar cases.

Key Words: Pediatric, ischemia, extremity, protocol.

Introduction

The femoral artery and vein are commonly used for vascular access in the pediatric population. They are relatively easy to cannulate, even in the very young, and their use avoids the use of other arteries and veins that may present more serious complications. However, ipsilateral ischemia of the distal lower extremity, although infrequent, is an important and devastating complication.

The current morbidity rate from intravascular catheters in the general pediatric population approaches 10% (1, 2) and the risk of accidental arterial puncture with attempted femoral cannulation is approximately 14% (3). In a majority of cases, this is successfully managed by withdrawing the needle or catheter and applying direct pressure.

Several surgical and nonsurgical treatment options exist for the management of acute lower extremity ischemia in the pediatric population. Unfortunately, there is no clearly defined subspecialty responsible for the management of pediatric vascular injuries, and because of the small incidence of vascular pathology in children, there is no field of pediatric vascular surgery. As a result, the task of caring for infants and small children with vascular injuries falls into the realm of the microsurgeon. The authors present several cases of distal lower extremity ischemia as a result of femoral artery catheterization and offer a protocol for the managing of similar cases (Fig. 1).

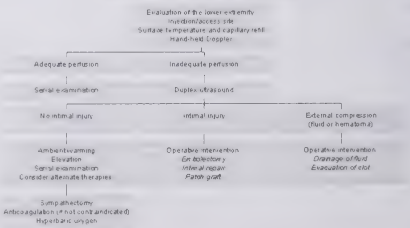
Management of Distal Ischemia in the Pediatric Population
Evaluation of the lower extremity
Injection/access site
Surface temperature and capillary refill
Hand-held Doppler
Adequate perfusion
Inadequate perfusion
Serial examination
Duplex ultrasound
No intimal injury
Intimal injury
External compression (fluid or hematoma)
Ambient warming
Elevation
Serial examination
Consider alternate therapies
Operative intervention
Embolectomy
Intimal repair
Patch graft
Operative intervention
Drainage of fluid
Evacuation of clot
Sympathectomy
Anticoagulation (if not contraindicated)
Hyperbaric oxygen

Fig. 1. Outline for management of acute pediatric lower extremity ischemia following catheterization.

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Case One

A 3-year-old female presented to the emergency department with significant abdominal trauma. The patient had been initially evaluated at an outside institution and transferred by helicopter. By report, the patient was a restrained, back seat passenger of an automobile that was involved in a head-on collision. She had no past medical or surgical history. On presentation, she was tachycardic and normotensive. Examination revealed abdominal distension and tenderness, and adequate distal lower extremity neurovascular supply. She was taken emergently to the operating room, where she underwent exploratory laparotomy, partial cecectomy and repair of serosal injury to the small intestine. In addition, a previously placed intraosseous tibial catheter was exchanged for a left femoral venous line and a right femoral arterial line. At the time, multiple prior attempts at right femoral access were noted.

Postoperatively, the patient was noted to have a markedly cool right foot with mottling of the skin and sluggish capillary refill. Doppler examination failed to document flow through the superficial femoral artery. The line was removed and the patient taken emergently to the operating room. She was noted to have full-thickness injury to the anterior surface of the common femoral artery, a clot within the lumen of the superficial femoral artery and a patent profunda femoris artery. A profundaplasty was performed using an ipsilateral saphenous vein (Fig. 2). Intraoperatively, she received 1,000 units of heparin and was maintained postoperatively on a therapeutic infusion for five days, at which time she was switched to daily aspirin. She has been seen at one year for follow-up with no adverse sequela.

Case Two

An 8-month-old infant presented for repair of tetralogy of Fallot. On the day prior to surgery, cardiac catheterization was performed via the right femoral artery. Following the procedure, the right lower extremity from the thigh to the toes was noted to be cooler and more mottled than the contralateral side. Conservative management, including ambient temperature warming, was successful in restoring adequate perfusion to the entire leg. The tetralogy of Fallot repair lasted ten hours, during which time continuous monitoring of the lower extremities was not possible. At the completion of the procedure, the right lower extremity was again noted to be cool and mottled. The patient was transferred to the pediatric intensive care unit for recovery and further evaluation.

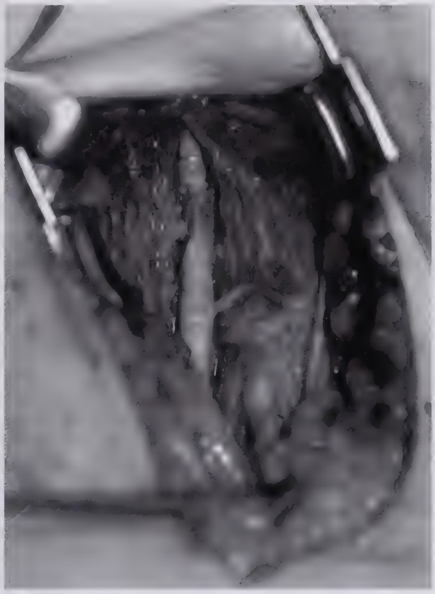

Fig. 2. Intraoperative photograph of a three-year-old female who developed acute lower extremity ischemia following multiple attempts at femoral vein cannulation. Profundaplasty was performed using an ipsilateral saphenous vein.

A hand-held Doppler was unable to identify a signal below the level of the femoral artery. An emergent ultrasound Duplex was obtained that revealed no evidence of mechanical obstruction at the level of the femoral artery. Runoff into the popliteal and posterior tibial systems was scant. The pediatric pain management service was consulted for sympathectomy.

A sympathectomy of the right lower extremity was performed using a nerve stimulator for localization. A setting of 4.0 mA was used in an attempt to locate the femoral nerve. Muscular twitches were markedly blunted due to the use of vecuronium for respiratory muscle paralysis. Six cc of 0.2% ropivacaine were injected via a 20-gauge, 50 mm needle at various points around the femoral nerve: 2 cc were placed medial to the nerve, 2 cc were placed lateral, and 2 cc were placed superficial.

Within the next hour, the warmth in the lower extremity returned and capillary refill in the toes improved. Over the ensuing 24-hour period, the vascular status of the leg remained stable and adequately perfused. A follow-up consultation for repeat sympathectomy was considered but not performed, based on the lasting effect of the first injection. The infant subsequently continued to recover from surgery and had no further episodes of distal ischemia.

Case Three

A 14-month-old male with Hirschsprung's disease presented with small bowel obstruction following initial colostomy and subsequent reconstruction seven months earlier. In the absence of improvement, he underwent exploratory laparotomy, lysis of small bowel adhesions, and resection of the gangrenous distal ilium, which had been trapped within an internal hernia. In addition, a left femoral arterial line was placed following completion of the procedure.

Several hours postoperatively, the left foot was noted to be cool on palpation and mottled in appearance as compared to the right foot. The arterial line was removed, the foot was elevated and a warming blanket was placed around the lower body. Within minutes, improvement in the temperature and appearance of the foot and toes was noted. A bedside Duplex study was performed that documented flow through the dorsalis pedis artery into the foot. The patient was not anticoagulated and continued to improve with conservative management.

Discussion

When a pediatric patient presents with lower extremity ischemia, a thorough history and examination of both lower extremities should be performed. Careful examination of the groin should document the level at which attempts at catheterization have been made and the number of skin puncture sites, which may be a marker for the amount of local soft tissue damage and/or ischemia that has been caused to the area. A search for underlying hematomas or seromas should be made to rule out mechanical compression as a cause of ischemia. Any change in skin temperature along the lower extremity—and between extremities—should be appreciated, and a measure of the temperatures at the level of the toes should be recorded. Capillary refill times should be noted in both the ipsilateral and contralateral extremity. The patient's fluid status should be evaluated and volume replaced as indicated, to correct poor inflow as a contributing factor to the distal ischemia. A hand-held Doppler should be used to document evidence of an arterial waveform at various levels in the lower extremity (femoral, popliteal, dorsalis pedis, and posterior tibial at the ankle).

The presence of adequate perfusion to the distal lower extremity would warrant continued conservative management as outlined below, including careful, serial examinations to identify any change from baseline. In the absence of adequate perfusion, urgent, bedside radiographic evaluation of the arterial inflow should be made by Doppler ultrasonography. This should be performed by an experienced technician looking for evidence of intimal injury, such as a flap, or significant hematoma that would indicate the need for operative intervention. In the absence of mechanical obstruction, several nonoperative strategies are available to improve blood distal perfusion.

Initial management should include increasing the ambient temperature of the extremity with a warming blanket and placing a temperature monitor on each foot to measure the difference in surface temperature over time. The extremity should be elevated to minimize edema formation and to promote venous and lymphatic return. Serial examinations, for such measures as surface temperature, capillary refill and Doppler signal, should be performed and any changes from the baseline examination documented.

Sympathectomy should be considered if Doppler imaging fails to identify intimal obstruction. The technique of caudal anesthesia, originally described in 1901, has since become a frequently used modality for children as well as adults. The use of sympathetic blockade to treat ischemic conditions in the pediatric population has been described in the literature (4, 5). The effect of sympathectomy is to improve local blood flow by vasomotor paralysis and the resultant decrease in peripheral vascular resistance. It may also decrease tissue demand for oxygen by blocking resting basal tone and spontaneous activity of the musculature. In the hand, sympathectomy in patients with Raynaud's phenomenon has been shown to increase digital blood flow 6–10 times (6).

Reasons for caudal anesthesia include diminishing the intraoperative anesthetic requirement and postoperative pain control. In the pediatric population, sympathetic blockade has been used to manage various causes of vascular insufficiency (7–9). It has also been used for vascular compromise in patients with Kawasaki disease (10). More appropriately, it has been used for lower extremity ischemia secondary to vascular cannulation (11). This technique may be more successful than others in improving limb survival in the pediatric population because total blood flow may not yet be affected by occlusive states, such as atherosclerosis and thromboembolism (12). In the present protocol, sympathectomy is used as an adjunct to heparinization. It does not need to be done instead of any of the other nonoperative modalities. It is recommended for patients with ischemia of a lower extremity and no obvious impedance to flow (intimal flap, extrinsic compression, etc.).

The complications of lumbar sympathectomy include bleeding, infection, hypotension, dural puncture, and the toxic effects of the infiltrated agent. It is therefore contraindicated in patients with bleeding disorders. For pediatric patients with acute ischemia of the lower extremities, sympathectomy provides a valuable tool in the overall management of their conditions; however, no formal protocol for this purpose has yet been outlined. Repeat sympathectomy should be considered if the initial response was favorable but a recurrence of ischemia is witnessed.

Hyperbaric oxygen therapy should also be considered, since it serves to increase the oxygen content of the blood. Hyperbaric oxygenation has become an important treatment option for a variety of anoxic conditions (13). It has been reported to be successful in the treatment of peripheral ischemia in infants due to disseminated intravascular coagulation (14). However, transfer to and monitoring within a hyperbaric chamber may be problematic for the severely ill patient.

Thrombolytic agents such as tissue plasminogen activator (tPA) and urokinase have been used safely in the pediatric population for a variety of indications, including occlusion of venous catheters and lysis of fibrin clots following orthotopic liver and kidney transplantation (15, 16). They are being used increasingly to treat pediatric cardiac disorders such as aortic thrombosis, right atrial thrombosis and pulmonary embolism, among others (17). The standard initial dose is 0.1–0.5 mg/kg/hour. However, Wang et al. reported that tPA in doses as low as 0.01 mg/kg/hour was effective in treating patients with acute thrombosis (18). Major bleeding occurred in only one infant although minor oozing was noted in 27% of the children. Ino et al. reported the use of thrombolytic therapy for femoral artery thrombosis following catheterization (19). A prospective evaluation of 526 patients was undertaken to evaluate the incidence of thrombosis and the role of thrombolytic agents. An initial bolus of 150 U/kg was given prior to arterial puncture. A second bolus of 50 U/kg was given only if the pulse was diminished two hours after the procedure. This was followed by an infusion of 20 U/kg/hour for no more than 48 hours. Thrombolytic agents were added to the regimen if the pulse in the affected leg was absent or reduced and if the systolic blood pressure was less than two-thirds that of the contralateral side. Forty-five patients (8.6%) were noted to have a diminished pulse after catheterization. Of these, 32 (71.1%) improved with systemic heparinization only; the remaining 13 patients (28.9%) were given thrombolytic therapy. This was successful in 11 cases and 2 patients required thrombectomy.

Conclusions

The decision for operative intervention in the pediatric population should not be taken casually. The age of the patient should be considered during the decision-making process. Younger patients have smaller vessels and may be more prone to postoperative thrombus formation despite adequate vascular repair and aggressive anticoagulation. Specific procedures depend on the nature of the injury. Simple clot removal or fluid evacuation does not require disturbance of the vessel and may be equally appropriate for neonates as well as infants and children. Intraoperative Doppler examination of the vessel should be used to note any changes in flow characteristics following a given maneuver. If exploration of the vascular system is warranted, general tenets of vascular surgery should be followed. Magnification using loupes or an operative microscope is usually warranted. Proximal and distal control of the injured vessel should be achieved first, followed by a bolus of heparin, before making an arteriotomy. Small caliber Fogarty catheters may be inserted proximally and distally to remove any intraluminal clot. Intimal flaps should be tacked back to the arterial wall and a patch of saphenous vein used to open areas of narrowing. More comprehensive damage may warrant excision of the affected area and re-anastomosis. Nonautogenous materials, such as ePTFE, should be avoided if possible in the growing child.

The protocol outlined above attempts to provide guidance in the management of pediatric patients with acute ischemia of a lower extremity following catheterization. It should not be considered absolute but rather be amended as new information becomes available. Both surgical and nonsurgical techniques should be considered and evaluation by a skilled microsurgeon should be sought in the face of vascular injury that will not resolve with conservative measures.

Acknowledgments

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An Intraluminal Leiomyoma of the Small Intestine Causing Invagination and Obstruction:

A Case Report

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Abstract

Leiomyomas are mostly of benign character and are rarely seen in the gastrointestinal (GI) system. They represent one subgroup of a group of tumors known as gastrointestinal stromal tumors (GIST). Although rarely seen, they are symptomatic tumors, and they comprise 20–30% of all benign GI tumors. Diagnosis is difficult because of their rarity and the absence of specific symptoms.

This is a case report of intestinal leiomyoma in a patient who was suffering with GI obstruction for more than 5 months. The tumor was discovered only after the appearance of intestinal obstruction. The patient underwent laparotomy for ileus of unknown etiology. Leiomyoma was diagnosed by pathologic analysis.

Key Words: Leiomyoma, invagination, obstruction.

Introduction

TUMORS OF THE SMALL INTESTINE comprise 1.7–6.5% of all gastrointestinal neoplasms (1). They are mostly benign and are uncommonly seen in clinical practice (1). Leiomyomas are the most common of all symptomatic small intestinal tumors, comprising 20–30% of all benign gastrointestinal tumors. Sixty-five percent of the tumors are located in the stomach, with 23% in either the jejunum, ileum or duodenum.

It is difficult to diagnose leiomyoma because of its rarity. Therefore, misdiagnosis can occur if a careful history and good examination are not performed. The two most frequently presenting symptoms are intermittent gastrointestinal (GI) bleeding and GI obstruction, in that order (2). Less commonly, one may see intestinal invagination.

In this paper, we report the diagnosis of a giant leiomyoma with invagination of the small intestine, to emphasize the importance of careful investigation of such lesions.

Case

A 72-year-old female patient was admitted to our hospital with a 6-month history of intermittent attacks of abdominal distention and pain, obstipation and constipation, and new onset of vomiting. She had a 15-year history of diabetes mellitus and a 10-year history of hypertension. The patient had been seen by a physician three months prior to admission for the aforementioned symptoms. At that time, colonoscopy was performed, with no diagnostic finding.

In our hospital, physical examination revealed abdominal distention and hyperactive bowel sounds. No significiant weight loss or palpable mass was identified. Rectal examination was normal. Biochemical studies were normal with the exception of white blood cells of 11,600/mm^3 (normal range: 4,300–10,800/mm^3) and hematocrit of 31% (normal range for females: 37–48%). Guaiac testing was negative three times.

Imaging studies included the following: abdominal x-ray showed air-fluid level, CT scan showed thickening of distal ileal wall and intraluminal mass lesion of soft tissue density, causing partial obstruction of small intestine in the right lower quadrant (Fig. 1), and enteroclysis showed a mass causing invagination with significant obstruction of the distal portion of the jejunum with dilatation proximal to it (Figs. 2 and

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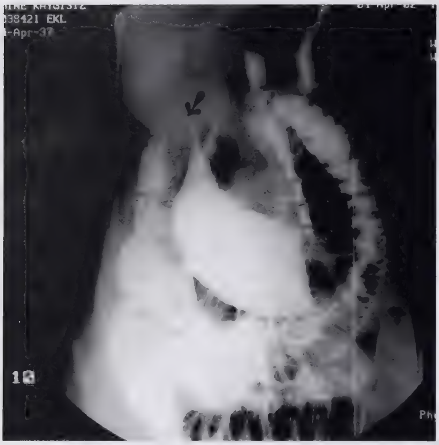

Fig. 1. The bird-beak appearance of small bowel segment on enteroclysis, which is typical for invagination (arrow).

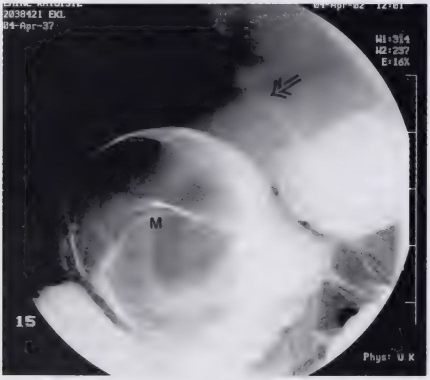

Fig. 2. The large intraluminal mass (M), which is seen as filling defect, causing invagination and obliteration of distal segment of small bowel on spot view taken at the level of invagination.

3). The patient's pain and abdominal distention increased, requiring emergent exploratory laparotomy surgery. This revealed a 5×3×2 cm polypoid intraluminal tumor as etiology of her invagination and obstruction (Fig. 4). Ileo-ileal anastomosis was performed after resection of the tumoral segment. No complication occurred in the early postoperative period, and the patient was discharged on the 14th postoperative day.

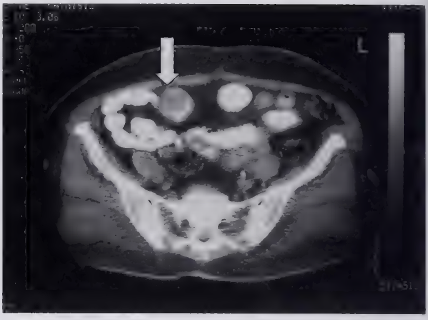

Fig. 3. Intraluminal leiomyoma causing invagination in ileum on CT.

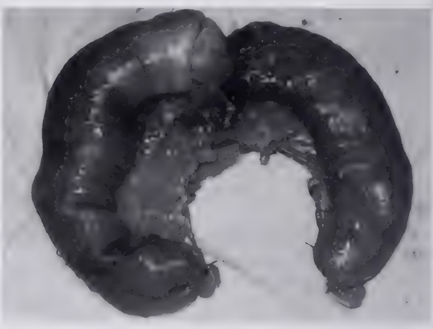

Fig. 4. Macroscopic appearance of the polypoid intraluminal tumor.

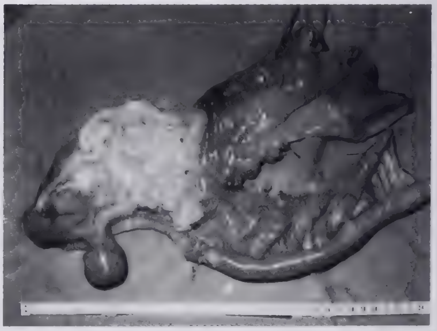

Fig. 5. Benign leiomyoma cells are seen.

Pathological investigation revealed leiomyoma of benign character (Fig. 5).

Discussion

Tumors of the small intestine are rare and generally benign. Leiomyomas comprise approximately one fourth of benign GI tumors and are the most common symptomatic benign tumors of the small bowel (3). They originate from the mesenchyma and arise from spindle cells of the muscular layer of the intestine.

These tumors have a peak incidence between 50–60 years of age. They are found most commonly in the jejunum but can also be found in the ileum and duodenum. Leiomyomas are usually an incidental finding during unrelated surgery but may be suspected in cases of GI bleeding or intussusception (4).

Leiomyomas show four different growth patterns: (a) intraluminal, (b) intramural, (c) extraluminal and (d) dumbbell shaped. The tumor is usually single, firm, grayish-white, well-defined, and encapsulated. Although most remain asymptomatic, non-specific complaints such as GI bleeding (most common symptom, with 65% frequency), intermittent abdominal pain or chronic anemia due to occult blood loss may be seen (2, 4).

In the case of this patient, the tumor was located intraluminally at the ileum. The patient also had a low hematocrit value, though guaiac test was negative.

Intussusception with intermittent intestinal obstruction is the second most common complication, with an incidence of 25–45%, especially in tumors located in the ileum (4). Invagination may also cause GI bleeding due to ischemia and necrosis of the tumor. Although our patient was slightly anemic, her main symptom was obstruction. Sometimes the tumor may enlarge enough to be palpable in an asymptomatic patient.

It is easy to overlook the correct diagnosis in cases of leiomyoma because of the patients' nonspecific complaints. Iron deficiency anemia and obstructive symptoms should alert the physician to examine the small intestine. An accurate diagnosis should include a good medical history, physical exam, specific imaging modalities such as CT enteroclysis, endoscopy and endoscopic ultrasound, scintigraphy, angiography and capsule endoscopy (1, 2). In most patients, the mean period between onset of complaints and diagnosis has been found to be seven months (5). However, the patient in this case report was correctly diagnosed after four months.

CT is very successful in detecting both primary and metastatic lesions and can show 90% of leiomyomas. While computerized tomography cannot differentiate benign from malignant tumors, malignant behavior can be assessed by size and biologic behavior (4, 6). Leiomyomas are sharply defined spheric or ovoid masses of homogeneous density and show contrast enhancement. They are seen as oval or round filling defects on barium studies, except extraluminal lesions, which may not be detected unless thay are quite large (6, 7). Sometimes central necrosis can be seen, making the differentiation more difficult.

The most reliable method of evaluating the malignancy potential of these tumors using histopathologic evaluation is by notable absence of mitosis (2). Mitosis is the most important criterion of malignancy (8).

In summary, early diagnosis of leiomyomas correlates with good prognosis for patients. A thorough evaluation is imperative to prevent late diagosis of leiomyoma and the resulting sequelae (4).

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Superior Vena Cava Syndrome (SVC Syndrome):

A Rare Cause of Conjunctival Suffusion

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Abstract

Obstruction of blood flow in the superior vena cava results in the signs and symptoms of superior vena cava (SVC) syndrome. Venous collaterals form, to establish alternative pathways for return of venous blood to the right atrium. The rapidity of onset of symptoms and signs from SVC obstruction is directly related to the rate at which obstruction occurs and how effective the formed collaterals are. Lung cancer and lymphoma account for more than 90% of cases of SVC syndrome. Recognition of signs and symptoms allows us to make an early diagnosis. Facial swelling, distended veins over the neck, upper extremity swelling, and dyspnea are common findings. Proptosis, periorbital swelling (including eyelid), conjunctival suffusion and elevated intraocular pressure are documented ophthalmic findings in SVC syndrome.

We present a rare case of conjunctival suffusion in a 72-year-old male diagnosed with superior vena cava syndrome secondary to lung cancer.

Key Words: Conjunctival suffusion, SVC syndrome, suffusion, SVC obstruction, lung cancer.

Introduction

OPHTHALMIC CHANGES in association with superior vena cava syndrome are rarely seen by an ophthalmologist. The diagnosis is usually made by an internist on the basis of history and common presenting signs and symptoms. In the medical literature, periorbital swelling, swelling of the eyelid and orbital proptosis are reported. SVC syndrome is a rare cause of conjunctival suffusion. We present a case report of conjunctival suffusion in a patient diagnosed with SVC syndrome.

Case Report

A 72-year-old male with a medical history of uncontrolled, insulin-dependent diabetes mellitus, hypertension, hypercholesterolemia, peripheral vascular disease, anemia, and 60-pack- year smoking was admitted to another hospital for uncontrolled diabetes and a fall. Later, he was discharged for follow-up by the Pulmonary Service at the Bronx Veteran's Affairs Medical Center, because of abnormal chest X-ray finding (Figs. 1 and 2).

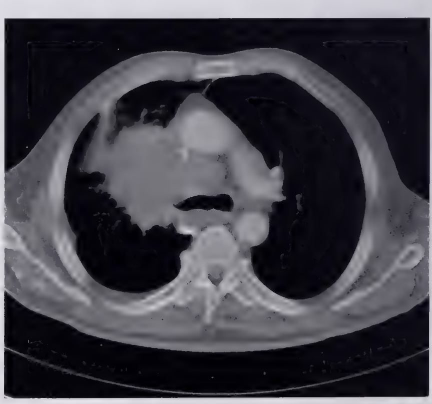

Fig. 1. Chest X ray showing right upper lobe mass involving the mediastinum, during inspiration.

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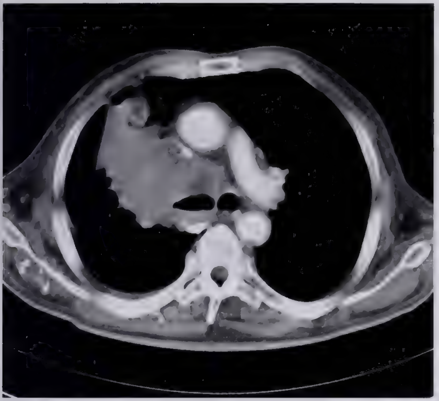

Fig. 2. Chest X ray showing right upper lobe mass involving the mediastinum, during expiration.

CT scan showed a 7 × 5.5 cm mass surrounding the pulmonary artery and trachea, with decreased flow in the subclavian vein and the superior vena cava. Bronchoscopic biopsy confirmed the diagnosis of small-cell lung cancer.

About a week after diagnosis of small-cell lung cancer, the patient presented in our emergency room with generalized weakness, shortness of breath, polyurea and increased thirst. He was admitted with a working diagnosis of diabetic ketoacidosis (DKA) secondary to noncompliance and postobstructive pneumonia in the right upper lobe. Repeat CT scan (Figs. 3 and 4) showed large right hilar and superior hilar mass, encasing the SVC and infiltrating the mediastinum around the right main stem bronchus and right pulmonary artery with mild subsegmental atelactesis within the right upper lobe.

The patient was admitted to the ICU. On examination, he was short of breath and had swelling of the upper extremities and chest, with prominent cutaneous veins over the neck and chest. His most remarkable feature was a suffusion of the conjunctiva (Figs. 5–8), and periorbital and facial edema. The patient denied any pain on eye movement, extraorbital movements were intact. He also denied any contact with an allergen. He was treated for DKA and postobstructive pneumonia.

The Ophthalmology Department was consulted. Their examination revealed intraocular pressure with Tonopen OD: 22, OS: 23; visual acuity with correction, OD: 20/50, OS 20/50; dilated fundoscopic examination showed no evidence of papilledema; overall examination results were within normal limits. Symptomatic treatment with artificial tears was advised.

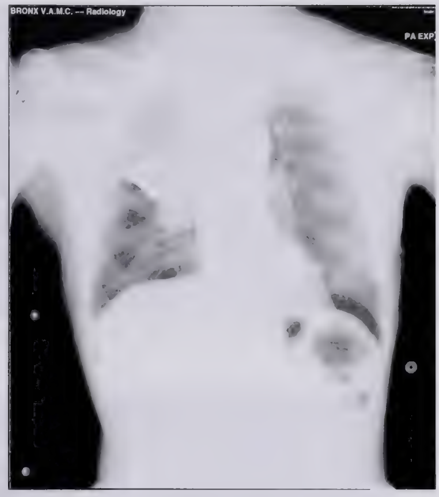

Fig. 3. CT scan (with contrast) showing right hilar mass with subtotal obstruction of superior vena cava.

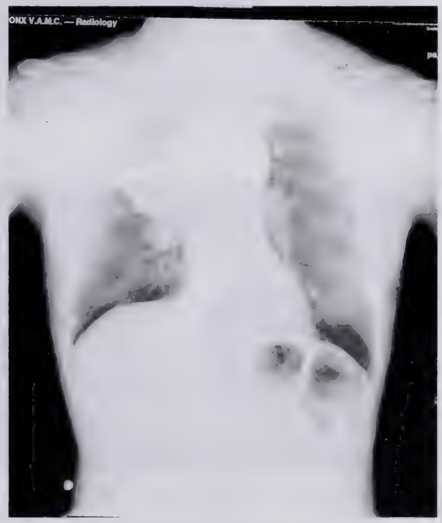

Fig. 4. CT scan (with contrast) showing superior hilar mass with subtotal obstruction of superior vena cava.

The patient was seen the same day by the Oncology Department and was started on radiation therapy (RT) and chemotherapy for palliative man-

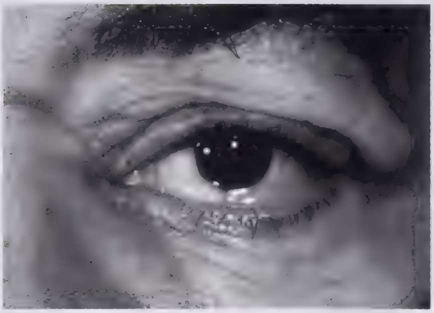

Fig. 5. Left eye, showing suffusion and periorbital swelling.

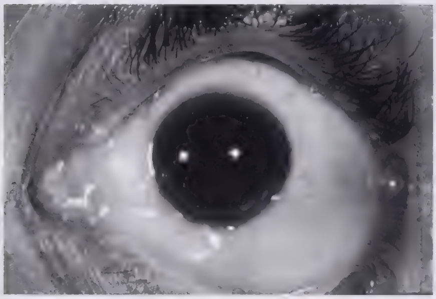

Fig. 6. Conjunctival suffusion, left eye.

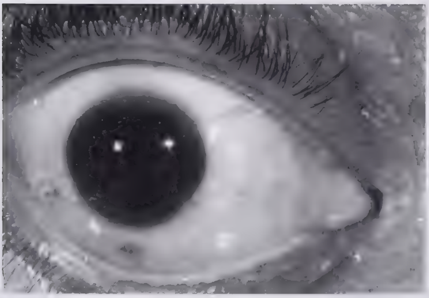

Fig. 7. Conjunctival suffusion, right eye.

agement of SVC syndrome. He improved clinically, and after 4 days of RT all signs of SVC syndrome had resolved. He was then transferred to the palliative care team for management and continuation of care.

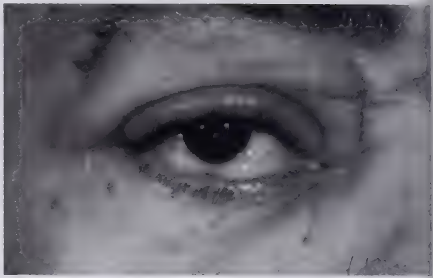

Fig. 8. Right eye, showing suffusion and periorbital swelling.

Comment

Recognition of signs and symptoms of the SVC syndrome helps in making early diagnosis and providing appropriate treatment. Venous engorgement over neck and chest, facial swelling (especially periorbital) (1, 2) and dyspnea are commonly noted signs and symptoms, which are directly related to the rapidity with which the obstruction occurs and the effectiveness of collaterals for returning venous blood to the right atrium. Periorbital swelling (eyelid) (3–5), conjunctival suffusion (6), orbital proptosis (7, 8), increased intraocular pressure (9) and blurring of vision have been documented in patients with SVC syndrome.

Venous drainage from the orbit occurs primarily via the superior and inferior ophthalmic veins. The ophthalmic veins eventually join together after passing through the superior and inferior orbital fissures, respectively, prior to entering the cavernous sinus. The venous blood is then drained via the sphenoparietal sinus, the superior petrosal sinus, the basilar plexus and the pterygoid plexus. All orbital venous blood eventually enters the superior vena cava for recirculation. Obstruction of the SVC has the potential to cause an outflow venous obstruction of the orbit, with resulting orbital congestion, chemosis or conjunctival suffusion as recently described, and increased intraocular pressure secondary to elevated episcleral venous pressure (10). In addition to SVC, the differential diagnosis of this outflow obstruction includes carotid cavernous fistula, dural venous sinus thrombosis and congestive heart failure. Outflow obstruction leading to orbital congestion can also occur as a result of a more localized orbital process including orbital varices, thyroid ophthalmopathy, orbital tumors or Sturge Weber syndrome.

The goal of medical management of SVC syndrome is rapid diagnostic investigation and administration of palliative radiotherapy to alleviate the symptoms. Most patients treated with radiotherapy respond subjectively in 72 hours and show objective signs of relief in 7 days (11). Medical management, including use of diuretics, head elevation, oxygen and low salt diet may help. Use of glucocorticoid may help alleviate symptoms by shrinking lymphoma masses. The management (medical or surgical) should focus on the correction of the underlying cause.

In a situation where radiotherapy or chemotherapy may not be indicated because of low likelihood of tolerance, due to side effects or refractoriness to treatment, the use of endovascular stents for palliative management can be considered. Improvement in symptoms usually occurs within 48 hours of stent placement, and most of the patients remain symptom-free until death.

In our patient, venous engorgement, conjunctival suffusion, and swelling of facial and upper extremity resolved completely after radiotherapy and chemotherapy, with symptomatic and clinical improvement. He was transferred to palliative care for continuation of care and management.

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Effects of N-Acetylcysteine on Methotrexate-Induced Small Intestinal Damage in Rats

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Abstract

Methotrexate (MTX) is known to cause damage to the small intestine, leading to its dysfunction. The aim of the present study was to examine whether the administration of N-acetylcysteine (NAC) provides protection against the MTX-induced damage to small intestinal epithelium in rats. A single dose of MTX (20 mg/kg, intraperitoneal) was followed by intraperitoneal saline or NAC administration (150 mg/kg, MTX+NAC group) for the next 5 days. Afterward, the rats were sacrificed and small intestinal segments were fixed for light microscopic examinations. Glutathione and malondialdehyde levels, myeloperoxidase, superoxide dismutase and catalase activities were measured in the other intestinal segments. MTX caused an increase in the levels of glutathione and malondialdehyde and in the activities of myeloperoxidase, superoxide dismutase and catalase. These changes were significantly reversed in MTX+NAC-treated rats. Light microscopy in the MTX group revealed mucosal damage, which decreased with NAC treatment. Our results confirmed that administration of NAC decreased the MTX-induced damage to the small intestine. This protective effect of NAC may have clinical applications in chemotherapy.

Key Words: Methotrexate, N-acetylcysteine, small intestine, histopathology.

Introduction

METHOTREXATE is classified as an antimetabolite drug, which means that it is capable of blocking the metabolism of cells. As a result of this effect, it has been found helpful in treating certain diseases associated with abnormally rapid cell growth, such as some cancers, psoriasis and rheumatoid arthritis.

MTX is also known to cause damage to the small intestine, leading to its dysfunction (1). Nausea, vomiting, diarrhea, stomatitis, decreased absorption and gastrointestinal ulceration are reported to occur after the use of this chemotherapeutic agent (2). Therefore, it is important to relieve the side effects of MTX-induced intestinal damage to perform chemotherapy effectively.

Increased oxidative stress and decreased antioxidant defenses have been demonstrated in intestinal mucosal biopsies of patients with MTX-induced damage to small intestinal epithelium. Therefore, this damage may be controlled by antioxidant agents. Beneficial effects of various antioxidants, such as vitamin A (3), lactoferrin (4), melatonin (5), prostaglandin E_1 (6) and garlic extract (7), have been shown in MTX-induced damage to small intestine.

N-acetylcysteine has been widely used as an antioxidant *in vivo* and *in vitro* (8–10). More recently, various experimental studies of NAC have shown it to be a powerful antioxidant and a potential therapeutic agent in the treatment of cancer (11), heart disease (12), colitis (13, 14) and pancreatitis (15), all of which are characterized by free radical oxidative damage. The present study was undertaken to determine whether NAC, as a potent free-radical scavenger, could ameliorate the oxidative damage of small intestinal mucosa induced by MTX.

Materials and Methods

Animals

Forty male Wistar-albino rats, 80–85 days old and weighing 240–280 g each, were obtained from

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Glossary

ANOVA = analyses of variance
CAPS = 3-cyclohexilamino-1-propane sulfonic acid
CAT = catalase
DTNB = 5,5'-dithio-bis 2-nitrobenzoic acid
EDTA = edetic acid
FD4 = average molecular mass
GSH = glutathione, reduced
INT = p-iodonitrotetrazolium violet
MDA = malondialdehyde
MPO = myeloperoxidase
MTX = methotrexate
NAC = N-acetylcysteine
NADP = nicotinamide adenine dinucleotide phosphate
NADPH = nicotinamide adenine dinucleotide phosphate, reduced
ROS = reactive oxygen species
SDS = sodium dodecyl sulfate
SOD = superoxide dismutase

Kahramanmaras Sutcu Imam University, School of Medicine, Experimental Research Laboratory (Kahramanmaras, Turkey). They were kept in stainless steel cages in the animal room, which was maintained on a 12 h light/12 h dark cycle at 21–22°C. The rats were allowed free access to food and water *ad libitum*. All rats fasted 24 h prior to the experimental procedure. The structure of this study and the animal experimental procedures were approved by the Ethical Committee of Kahramanmaras Sutcu Imam University School of Medicine.

Experimental Procedure and Treatment Protocols

MTX (Wyeth Lederle Ltd., Tokyo, Japan) and NAC (Husnu Arsan Drug Company, Istanbul, Turkey) were injected intraperitoneally. Following a single dose of methotrexate (20 mg/kg), either saline (MTX group) or NAC (150 mg/kg, MTX+NAC group) was administered for the next 5 days. In other rats, following a single injection of saline, saline (control group) or NAC (150 mg/kg, NAC group) was injected for the next 5 days. Then the animals were killed by decapitation and tissue samples from the small intestine were taken for biochemical analysis and histopathology.

Preparation of Homogenate

As soon as the experimental rats were sacrificed, their intestinal tissues were quickly removed and blotted on filter paper. Tissue samples were homogenized with 10 volumes of ice-cold 0.25 mol sucrose and centrifuged in 14,000g to measure the activities of antioxidant enzymes and myeloperoxidase (MPO) and the levels of reduced glutathione (GSH) and malondialdehyde (MDA) in the resulting supernatant.

Biochemical Analysis

Superoxide dismutase (SOD) activity in the tissue was measured according to the method described by Fridovich (16). This method employs xanthine and xanthine oxidase to generate superoxide radicals, which react with p-iodonitrotetrazolium violet (INT) to form a red formazon dye. The dye was measured at 505 nm. Assay medium consisted of the 0.01 mol phosphate buffer and 3-cyclohexilamino-1-propane sulfonic acid (CAPS) buffer solution (50 mmol CAPS, 0.94 mmol edetic acid [EDTA], and saturated NaOH) with a pH of 10.2. SOD activity was expressed as U/mg protein.

Catalase (CAT) activities in the tissue were determined by measuring the decrease in hydrogen peroxide concentration at 230 nm by the method of Beutler (17). The assay medium consisted of 1 mol Tris HCI, 5 mmol Na_2EDTA buffer solution (pH 8.0), 1 mol phosphate buffer solution (pH 7.0), and 10 mmol H_2O_2. CAT activity was expressed as U/mg protein.

GSH level was determined according to the method of Beutler (17). The reaction mixture contained filtrate, phosphate buffer and 5,5'-dithio-bis 2-nitrobenzoic acid (DTNB) in a total volume of 10 mL. A blank was also prepared by using precipitating reagent and distilled water instead of filtrate. The absorbances were immediately read in a spectrophotometer at 412 nm before and after addition of DTNB. The values were determined from the standard curve. GSH level was expressed as μmol/mg protein.

MPO activity was determined by a modification of the O-dianisidine method (18). The assay mixture, in a cuvette of 1 cm path length, contained 0.3 mL 0.1 mol phosphate buffer (pH 6.0), 0.3 mL 0.01 mol H_20_2, 0.5 mL 0.02 mol O-dianisidine (freshly prepared) in deionized water and 10 microliter of supernatant in a volume of 3.0 mL. The supernatant was added, and the change in absorbance at 460 nm was observed for 10 min. All measurements were carried out in duplicate. One unit of MPO was defined as that giving an increase in absorbance of 0.001 per min, and specific activity was expressed as U/mg protein.

Lipid peroxidation level in the tissue samples was expressed by MDA. It was measured according to the procedure of Ohkawa et al. (19). The reaction mixture contained 0.1 mL tissue sample, 0.2 mL of 8.1% sodium dodecyl sulfate (SDS), 1.5 mL of 20% acetic acid and 1.5 mL of 0.8% aqueous solution of thiobarbituric acid. The mixture pH was adjusted to 3.5, the volume was finally increased to 4.0 mL with distilled water, and 5.0 mL of a mixture of n-butanol and pyridine (15:1, v/v) was added. The mixture was shaken vigorously. After centrifugation at 4,000 rpm for 10 min, the absorbance of the organic layer was measured at 532 nm. MDA level was expressed as nmol/mg protein.

All chemicals were obtained from the Sigma Chemical Corporation (St. Louis, MO, USA) with the exception of NAC, which was from Bilim (Husnu Arsan Drug Company, Istanbul, Turkey).

Histopathological Analyses

Small intestinal tissue specimens for histological examination were fixed in 10% formalin, embedded in paraffin wax on the oriented edge, and cut into 5 μm thick sections. All tissue sections were stained with hematoxylin and eosin for histological examination. In all groups, measurement of intestinal damage was assessed by scoring each of the following histopathological observations as 0, none; 1, mild; 2, moderate; 3, severe: (a) villous shortening and fusion; (b) epithelial atrophy; (c) crypt loss; (d) inflammatory infiltrate in the lamina propria and (e) goblet cell loss. Thus, the maximum total score was 15.

Statistical Analyses

Analyses of variance (ANOVA) followed by Tukey's multiple comparison tests were used to evaluate the groups of data. For all analyses, an associated probability (p value) of <0.05 was considered statistically significant.

Results

MTX treatment induced diarrhea in MTX-treated rats. Histopathological findings in MTX and MTX+NAC-treated groups are summarized in Table 1. MTX administration caused villous shortening and fusion, epithelial atrophy, crypt loss, inflammatory infiltrate in the lamina propria, and goblet cell depletion in small intestinal tissue (Fig. 1A). Significant histologic improvement was observed in the small intestine with NAC supplementation (Fig. 1B). The histopathological scores are presented in Table 2. The scores of the MTX group were significantly different from those of the control, MTX+NAC and NAC groups.

To examine the oxidative stress and inflammation in MTX-induced intestinal damage, we determined the levels of MDA and MPO activity in the small intestinal tissue homogenates of the rats. MTX treatment significantly increased MPO activities and MDA levels in comparison with controls. NAC administration to the MTX-treated rats significantly reduced the MPO activities compared to those in the MTX-treated groups without NAC. No statistically significant difference was found between the NAC groups (Fig. 2). On the other hand, it was also shown that the increased levels of MDA due to MTX decreased following the addition of NAC treatment (Fig. 3).

Antioxidant activities were investigated through the levels of tissue GSH, SOD, and CAT. MTX treatment significantly increased GSH levels and SOD and CAT activities in small intestinal tissue. However, supplementation of NAC to MTX-treated rats significantly decreased those antioxidant levels in intestinal tissue (Table 2).

TABLE 1
Histopathological Changes and Number of Exposed Rats in MTX and MTX+NAC-Treated Groups

Histopathologic Changes	MTX Group (n=10)			MTX +NAC Group (n=10)			
	Mild	Moderate	Severe	Absent	Mild	Moderate	Severe
Villous shortening and fusion	5	3	2	1	7	1	1
Epithelial atrophy	6	2	2	2	6	2	-
Crypt loss	5	3	2	5	4	1	-
Inflammatory infiltrate in the lamina propria	6	2	2	1	6	2	1
Goblet cell loss	6	3	1	4	4	2	-

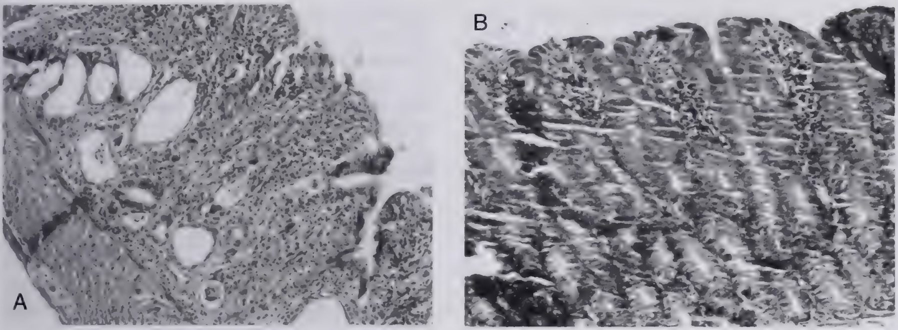

Fig. 1. Representative histological slides from rats in the MTX (**1A**), and MTX + NAC (**1B**) treatment groups. The small intestine was cut, embedded in paraffin, and then stained with H&E. Note villous shortening and fusion, epithelial atrophy, crypt loss, inflammatory infiltrate in the lamina propria, and goblet cell depletion in small intestinal tissue (**1A**). The histological changes were significantly improved by NAC treatment, as seen in a sample from the MTX+NAC group (**1B**). (Original magnification, 20×)

Discussion

Gastrointestinal toxicity is one of the most serious side effects of MTX treatment. It has been demonstrated that MTX treatment in rats induces several kinds of damage, such as increased permeability of poorly absorbable marker, fluorescein isothiocyanate-labeled dextran 4400 (FD4; average molecular mass, 4.4 KDa), suppression of intestinal absorption of glucose and neutrophil infiltration in intestinal lesions (6, 20). On the other hand, oxidative stress is known to be involved in several diseases and to be the cause of toxicity of many drugs. Gao et al. recently detected reactive oxygen species (ROS) production in the small intestine of MTX-treated rats, which was related to neutrophil infiltration, using chemiluminescence (21). Thus, oxidative stress probably plays an important role in MTX-induced intestinal toxicity. The present study focused on oxidative stress and histopathological changes, in order to understand the mechanism of MTX-induced small intestinal toxicity.

Chemotherapy commonly produces structural and functional damage to the intestinal mucosa in cancer patients (22) and in patients with rheumatoid arthritis (23). As a result of mucosal barrier damage, a common side effect of anticancer drugs is severe enterocolitis. In correlation with previous studies (5, 24), the results of the present study revealed that MTX-induced small intestinal injury is characterized by villous shortening and fusion, epithelial atrophy, crypt loss, inflammatory infiltrate in the lamina propria, and goblet cell depletion in small intestinal tissue. In experimental studies, NAC has been shown to be effective in reducing mucosal damage in colitis (13, 25) or gastric injury

TABLE 2

Effect of NAC on MTX-Induced Changes in Antioxidant Parameters and Histopathological Scores of Small Intestinal Tissue

Parameters and Scores	**Control group (n=10)**	**MTX group (n=10)**	**MTX + NAC group (n=10)**	**NAC group (n=10)**
CAT (U/mg protein)	0.14±0.02	0.35±0.07[1]	0.09±0.02	0.05±0.02
SOD (U/mg protein)	1.98±0.54	4.63±0.84[2]	3.53 ± 0.67[3]	2.72±0.94
GSH (μmol/mg protein)	0.004±0.001	0.018±0.006[1]	0.01±0.002	0.007±0.002
Histopathologic score	0.80±0.42	8.10±3.51[4]	5.10±2.90	1.10±0.56

Note. Data are presented as mean±SD.

[1] $p<0.001$, significantly different from control, MTX+NAC and NAC groups.

[2] $p<0.05$, significantly different from control and NAC groups.

[3] $p<0.05$, significantly different from MTX group.

[4] $p<0.05$ significantly different from control, MTX+NAC and NAC groups.

(26). And in response to the inflammation formed in the intestinal tissue by indomethacin, the beneficial effect of NAC through regulating microcirculation has also been shown (27). In addition, in a study of experimental intestinal ischemia-reperfusion, protective effects of NAC have been shown histopathologically and biochemically (28). Histopathological findings of our study showed that NAC ameliorates the mucosal destruction and supports the preservation of the intestinal epithelial morphology.

Antioxidant activities are important in the regulation of the gastrointestinal system. Antioxidant enzyme activities have been reported to increase or decrease in many inflammatory diseases. The protective roles of glutathione and GSH-dependent enzymes against noxious compounds in the gastrointestinal tract have been documented (29). Additionally, the local protective effect of SOD on intestinal epithelium was shown in an experimental study (30). In NSAID-induced intestinal toxicity, SOD and glutathione peroxidase activities decreased in relation to the severity of damage (31, 32). On the other hand, in acetic acid-induced colitis, an increase in SOD and CAT activities was detected (33). In our study, GSH, SOD and CAT levels increased in intestinal mucosa by MTX administration. The increase in antioxidant levels was thought to be a response of the living body to the oxidative stress induced by MTX and also to be a cause of MTX-induced oxidative damage. Thus, the MTX treatment of rats was shown to cause oxidative stress in intestinal mucosa. The increase in antioxidant levels was shown to be suppressed with the application of NAC, and thus it was demonstrated to lessen the response to the oxidative stress.

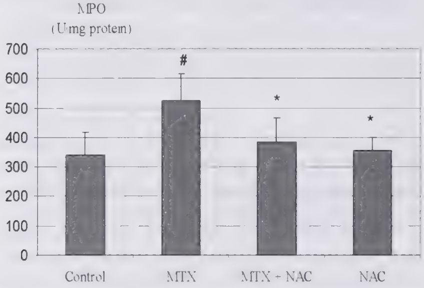

Fig. 2. Effects of NAC on small intestinal myeloperoxidase (MPO) activity.

$^{\#}$ p<0.001, MPO activity of MTX-treated group compared to that of control group. * p<0.05, MPO activity of MTX+NAC and NAC treatment groups compared to that of MTX-treated group. Results are mean ± SD; n=10.

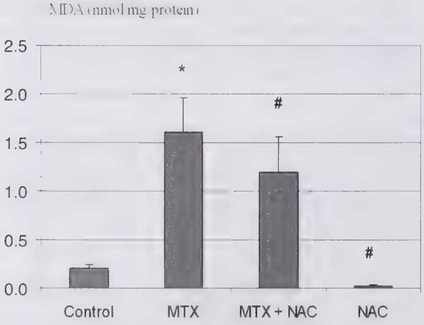

Fig. 3. Effects of NAC on small intestinal malondialdehyde (MDA) levels.

* p<0.001, MDA levels of MTX-treated group compared to that of control group. $^{\#}$ p<0.01, MDA levels of MTX+NAC and NAC treatment groups compared to that of MTX-treated group. Results are mean ± SD; n=10.

It is increasingly apparent that lipid hydroperoxide may play an important role in mediating cellular and molecular events in degenerative pathophysiological processes that lead to intestinal disorders (34). MDA is frequently used in the measurement of lipid peroxide levels, and it does provide a good correlation with the degree of lipid peroxidation. In the study of experimental diabetes induced by streptozotocin, it has been shown that the products of lipid peroxidation increased significantly in the small intestine owing to the oxidative stress (35). In another study, cisplatin was shown to increase the levels of MDA in the small intestine, and this increase in turn was depressed by an antioxidant, L-carnitine (36). On the other hand, in a study investigating the effects of MTX on small intestinal tissue, it was found that MTX markedly increased the levels of MDA and this increase was suppressed by melatonin (5). In our study, MDA levels in the small intestinal mucosa of MTX-treated rats were also found to be markedly increased, suggesting that MTX treatment caused oxidative damage and lipid peroxidation in intestinal mucosa. Increased levels of MDA were shown to decrease significantly after NAC administration. This finding may indicate that NAC can provide protection against the lipid peroxidation in the intestinal tissue induced by MTX.

It has been proposed that inflammation of gut mucosa causes impairment of antioxidant defense mechanisms, and makes tissue more susceptible to mechanisms, and makes tissue more susceptible to oxidative damage (37). In some recent studies it has been shown that neutrophil accumulation increases in inflammatory lesions of gut mucosa in patients with inflammatory bowel disease (38, 39). It has been demonstrated that activated neutrophils secrete enzymes, including MPO, elastase and other proteases. MPO plays a fundamental role in oxidant production by neutrophils and has been used as an effective quantitative index of inflammation due to the correlation between MPO activities and the histological analysis of neutrophil infiltration (40). In our study, elevated MPO levels indicated that neutrophil accumulation contributes to MTX-induced oxidative small intestinal injury. The decrease in the levels of MPO (elevated owing to MTX administration) with the treatment of NAC demonstrates that NAC has a preventive effect on MTX damage through the inhibition of neutrophil infiltration.

MTX inhibits cytosolic nicotinamide adenine dinucleotide phosphate (NADP)-dependent dehydrogenase and NADP malic enzyme, decreasing intracellular levels of reduced nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is necessary for glutathion reductase, which protects the levels of GSH, an important cytosolic antioxidant substance. Our present study is the second one to investigate the effects of NAC against the oxidative small intestinal injury induced by MTX. Our results have similarities with the other study (41). However, although the study of Miyazono et al. reported that GSH levels decreased with the administration of MTX, we found that GSH levels increased and that this increase was suppressed by NAC. In the study mentioned, MTX was given intravenously, but we administered it intraperitoneally. The reason for the increase in GSH levels in our study is probably due to the different route of administration and/or low dose of MTX. The issue of dosage effect might be resolved by comparing the effect of different doses and/or different routes of administration of MTX in rats.

Conclusion

The histopathological and biochemical results of the present study demonstrate that administered NAC is capable of reducing MTX-induced oxidative intestinal toxicity. These data indicate that NAC may be of therapeutic use in preventing enteritis in patients receiving chemotherapeutic agents. And overcoming the intestinal side effects of chemotherapy, such as diarrhea and malabsorption, may improve the effectiveness of the use of chemotherapeutic agents.

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An Unusual Post-traumatic Case of Extrahepatic Bile Duct Compression

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Abstract

Jaundice and cholestatic disease by external bile duct compression may be caused by several conditions, including pancreatic masses, portal cavernoma, Ormond's disease, metastases from gallbladder cancer, neurinomas, and hydronephrotic kidney.

We report a case of bile duct compression in a 56-year-old man with a known small (28 mm) right renal cyst and crossed, fused renal ectopia. The patient had a history of recent abdominal trauma due to a motorcycle accident and recurrent septic-type fever and jaundice. He also reported a weight loss of 5 kg in the last two months.

Abdominal ultrasonography showed intra- and extra-hepatic bile duct dilatation, and computed tomography scan showed hydronephrosis, dilatation of intra- and extra-hepatic biliary tract, and a right renal complex cyst of more than 9 cm. One can hypothesize a relationship between the abdominal trauma and the increase in size of the renal cyst, which, moreover, had changed its original shape.

The patient underwent cefuroxime and metronidazole therapy, with complete recovery from the cholangitis within one week. The treatment of choice would have been surgical excision or, alternatively, an image-guided percutaneous aspiration of the cyst, in order to avoid further episodes of cholangitis. Unfortunately, the patient refused either surgical or more conservative treatment and was lost to follow-up.

Key Words: Bile duct compression, abdominal trauma, renal cysts.

Case Report

A 56-YEAR-OLD MAN, a motorcycle driver, was admitted to our department with pruritus, jaundice and septic-type fever, and temperature peaks between 38°C and 39.7°C at 12-hour intervals. He had had a motorcycle collision two months before. The computed tomography (CT) scan performed at the time of the accident showed a crossed, fused renal ectopia with a right kidney cyst of 28 mm in size, and no evidence of abdominal hemorrhage, bile duct compression or dilatation of the intra-hepatic biliary tract (Fig. 1). The routine laboratory data were normal.

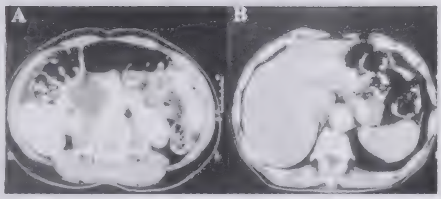

Fig. 1. Contrast axial CT scan in patients with crossed, fused renal ectopia showing a right kidney cyst of 28 mm. No signs of intra-abdominal hemorrhage, choledochus compression or dilatation of the intra-hepatic biliary tract are evident.

On clinical examination the patient reported a weight loss of 5 kg in the previous two months. Laboratory data revealed leukocytosis (12,500 per microliter), moderate anemia, and an increase of serum bilirubin (39 μmol/L), aspartate aminotransferase (102 U/L), alanine aminotransferase (97 U/L), and alkaline phosphatase (161 U/L). Blood and urinary cultures were negatives. Electrocardiogram and chest X-ray were normal. Abdominal ultrasonography confirmed the crossed, fused renal ectopia with right renal hydronephrosis, and showed a dishomogeneous renal cyst of 92 mm, causing compression and dilatation (17 mm) of the choledochus (Fig. 2). CT scan confirmed hydronephrosis, dilatation of intra- and extra-hepatic biliary tract, and a right renal complex cyst (Fig. 3). These data suggested a diagnosis of cholangitis due to an external compression of the choledochus. One can hypothesize a relationship between the abdominal trauma and the increase in size of the renal cyst, which, moreover, had changed its original shape and structure.

The patient underwent cefuroxime (1.5 g every 8 h) and metronidazole (0.5 g every 8 h) therapy, with complete recovery within one week. He refused either surgical or more conservative treatment, and was discharged with our advice to take prophylactic antibiotic therapy when necessary.

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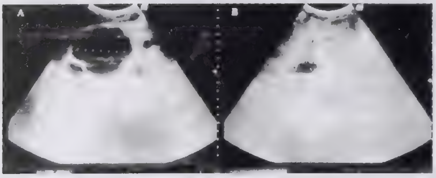

Fig. 2. Abdominal ultrasonography showing the crossed, fused renal ectopia with right renal hydronephrosis, and a dishomogeneous renal cyst of 92 mm causing compression and dilatation (17 mm) of the choledochus.

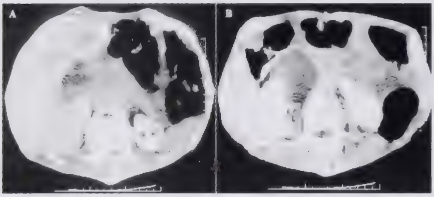

Fig. 3. Axial CT scan. Hydronephrosis, dilatation of intra- and extrahepatic biliary tract, and a right renal pseudocyst are confirmed.

Discussion

External compression of the biliary tract can be due to several conditions involving both the pancreas and the common bile duct, including portal cavernoma, Ormond's disease, metastases from gallbladder cancer, neurinomas, and hydronephrotic kidney (1–7). Several unusual cases of benign extrinsic compression of the common bile duct have been reported, including hydronephrotic kidney, direct compression by a duodenal diverticulum, abdominal aortic aneurysm, and portal vein thrombosis (3, 8–11). Several cases of both congenital and secondary biliary tract dilatation in patients with autosomal dominant or recessive polycystic kidney disease have been reported, although biliary tract obstruction is rare in children (12–15). The intrahepatic tract dilatation is never due to mechanical compression on the choledochus by renal cysts, but rather by a malformation of the biliary tract itself, associated with polycystic disease of the kidney. No biliary tract compression and jaundice caused by post-traumatic renal pseudocyst have been described.

Patients with renal cysts should usually undergo percutaneous aspiration and ethanol sclerotherapy, or anterograde or retrograde endoscopic procedures, which represent minimally invasive techniques as alternatives to open and laparoscopic surgery (16, 17). Percutaneous transparenchymal endocystolysis, as a first-line therapy, has also been suggested (18).

In conclusion, in the presence of bile duct compression, jaundice and septic-type fever due to the (probably post-traumatic) increase in size of a preexistent renal cyst, the treatment of choice should be surgical excision or, alternatively, an image-guided percutaneous aspiration of the cyst.

This strategy could have been useful in order to prevent further episodes of cholangitis in our patient. Unfortunately, despite our suggestions, he refused any treatment and was lost to follow-up.

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Erythrocytosis in a Patient on Hemodialysis for Thirteen Years

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Abstract

Most hemodialysis patients exhibit renal anemia mainly due to erythropoietin deficiency as a result of impaired erythropoetin production in the kidney. However, erythrocytosis in patients with renal failure requiring hemodialysis is extremely rare. We report the development of erythrocytosis in a patient with a polycystic kidney disease on hemodialysis for 13 years. She had erythrocytosis with increased serum erythropoietin levels despite severe secondary hyperparathyroidism, which is known to depress erythrocytosis. Since neither renal disease (renal cell carcinoma) nor extrarenal diseases (hypoxia, hepatoma, cerebellar diseases) linked with erythropoietin production could be proven, this case might be one with inappropriate idiopathic erythropoietin production after 13 years of hemodialysis, the longest duration of dialysis in the literature before erythrocytosis was observed.

Key Words: Erythrocytosis, hemodialysis, polycystic kidney disease, polycythemia.

Introduction

MOST HEMODIALYSIS PATIENTS exhibit renal anemia mainly due to erythropoietin (EPO) deficiency as a result of impaired EPO production in the kidney. In a minority of these patients, hematocrit values above 35% are observed without recombinant human erythropoietin (rHuEPO) therapy. The primary site of production of EPO is the kidney, although serum EPO is detectable in surgically anephric patients. In these cases, extrarenal EPO is most probably produced in the liver. Diminished EPO production has been considered the primary cause of anemia in renal disease. However, acording to recent reports using immunological assay, EPO levels have been reported to be elevated and normal as well as decreased in the serum of renal failure patients (1–3).

Erythrocytosis may complicate the course of various renal diseases, presumably through increased renal production of erythropoietin. These diseases include benign and malignant tumors, simple cysts, hydronephrosis, renal artery stenosis and polycystic kidney disease (4–7). Erythrocytosis has also been reported after renal transplantation (8). However, erythrocytosis in patients with renal failure requiring maintenance dialysis is extremely rare (9–15). We report the development of erythrocytosis in a patient with polycystic kidney disease and on hemodialysis for 13 years.

Case Presentation

A 50-year-old woman was diagnosed in 1992 as having chronic renal failure due to polycystic kidney disease (PKD). The patient had been maintained by routine hemodialysis without complications since then. She had no history of lung disease, alcoholism, tobacco use or coronary artery disease. During the previous three months, the patient began to complain of numbness in her hands. Medications at that time consisted of calcium acetate and nonsteroid anti-inflammatory drugs. Physical examination showed an alert, normotensive, obese woman with a body mass index of 32 kg/m^2. Representative laboratory test results showed the following values: serum urea

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nitrogen, 21.3 mmol/L; serum creatinine, 798 μmol/L; calcium, 2.35 mmol/L; phosphorus, 0.96 mmol/L; and serum alkaline phosphatase, 16.8 nkat/L. Liver function studies were normal, and hepatitis B surface antigen, antihepatitis C antibody and antiHIV antibody were negative. The intact parathyroid hormone level was elevated to 1,032 ng/L. Hematologic profile disclosed a hemoglobin level of 10.4 mmol/L and a hematocrit reading of 51.2%. The white blood cell count was 7.3×10^9/L and the platelet count was 208×10^9/L. The serum erythropoietin level by immunoassay was increased to 33.3 mU/mL (normal 8–17 mU/mL).

The patient had had erythrocytosis (hemoglobin level more than 9.25 mmol/L) for one year and she had been anemic before then. She had been given erythropoietin therapy until the previous year. Neither iron nor EPO treatment had been provided to the patient for one year. Arterial blood gas study results on room air were as follows: pH, 7.40; Pco_2, 34.5 mm Hg; Po_2, 88.2 mmHg; and O_2 saturation, 96%; there was no evidence of hypoxia. Cranial computed tomography revealed normal findings, cerebellar hemangioblastoma was not found. In abdomen tomography, multiple cysts were found in the liver and kidneys without evidence of renal or extrarenal site of EPO production such as hepatoma or renal cell carcinoma. Thorax tomography was also normal. For evaluation of extrarenal diseases linked with erythrocytosis, upper gastrointestinal endoscopy was performed. A gastric ulcer was found and biopsy revealed chronic gastritis.

Discussion

This patient with end-stage renal disease secondary to polycystic kidney disease developed erythrocytosis after 13 years. She had high serum levels of erythropoietin according to sensitive radioimmunoassay. Increased blood levels of erythropoietin have been previously reported in some anemic patients with chronic renal failure (16), showing that end-stage kidneys are capable of augmenting the secretion of biologically active erythropoietin. Elevated erythropoietin levels may still be lower than those seen in nonuremic patients with comparable degrees of anemia (16). Excessive renal erythropoietin secretion in the presence of erythrocytosis may result from disturbances in the normal feedback control system or from unregulated, autonomous hypersecretion. It is believed that an intrarenal oxygen sensor regulates renal erythropoietin secretion to maintain the erythrocyte volume needed for optimal tissue oxygenation (17).

Elevated erythropoietin levels in this patient may have resulted from autonomous or inappropriate renal secretion or extrarenal production. Tomography with contrast excluded any malignant transformation of renal cysts. In addition there was no evidence of chronic hypoxemia, decreased arterial oxygen saturation, cerebeller disease, hepatoma or other nonrenal diseases linked with the erythrocytosis (4, 18). Polycythemia vera was deemed unlikely without leukocytosis, thrombocytosis and splenomegaly, especially with an elevated erthropoietin level (19). It has been suggested that severe secondary hyperparathyroidism may depress hematopoiesis in chronic renal failure (20). Yet in spite of significant secondary hyperparathyroidism, our patient was seen to have erythrocytosis after 13 years of hemodialysis. Since neither renal nor extrarenal EPO production could be proven, this case may be one with inappropriate idiopathic EPO production, which could be a result of stimulus on hepatic cells by metals such as cobalt, nickel and manganese (20).

Yokoyama and colleagues reported a patient on peritoneal dialysis with erythrocytosis secondary to circulatory insufficiency due to chronic severe hypotension, which was hypothesized to lead to decreased oxygen supply to peripheral tissues and to stimulate EPO production (21). One other patient was reported to have congenital heart disease and persisting hypoxia accompanied with end-stage renal disease. In that case, overproduction of erythropoietin was explained by hypoxia (10). Shalhoub et al. reported two patients who developed polycythemia 5 and 7 years (respectively) following dialysis, secondary to elevated EPO levels secondary to acquired cystic disease of end-stage kidneys (9). Vereerstraeten and colleagues reported three patients on chronic maintenance hemodialysis with hematocrit values between 40–45% secondary to endogenous erythropoietin secretion (22). Erythrocytosis with bilateral hydronephrosis and secondary to polycythemia vera in patients with renal failure was also reported (13–15, 23). Krivoshiev and colleagues reported transient polycythemia in a 29-year-old hemodialysis patient after parathroidectomy for secondary hyperparathroidism (parathormone level declined from 900 to 21 pg/mL after surgery) (24). Shih and Leu reported five patients with renal failure undergoing maintenance hemodialysis (25). Three of them had leukocytosis, thrombocytosis, splenomegaly and formation of endogenous erythroid colonies in bone marrow with the diagnosis of polycythemia vera. The other two developed polycythemia 4 years after initiation of hemodialysis. Increased erythropoietin production in these patients has been diagnosed as inappropriate idiopathic EPO production due to a defect in the renal oxygen sensor.

In this article, we have reported another case of erythrocytosis following hemodialysis, due to endogenous erythropoietin production. This patient was normotensive patient with no signs of circulatory failure or hypoxia, yet she developed erythrocytosis despite severe secondary hyperparathroidism 13 years after initiation of hemodialysis, and in 12 months of follow-up, no other cause of secondary erythrocytosis was found.

Summary

Erythrocytosis in a patient on hemodialysis should prompt testing for polycythemia vera, renal cell carcinoma, hypoxia, circulatory failure, hepatoma, and cerebellar diseases. After all these diseases are ruled out, inappropriate idiopathic erythropoietin production can be diagnosed. This case is unique as the patient developed erythrocytosis due to inappropriate idiopathic erythropoietin production after 13 years of hemodialysis, the longest duration of dialysis in the literature before erythrocytosis was observed, and despite severe secondary hyperparathyroidism, which is known to depress erythropoiesis.

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Soil-Transmitted Helminths and *Plasmodium falciparum* Malaria:

Epidemiology, Clinical Manifestations, and the Role of Nitric Oxide in Malaria and Geohelminth Co-infection. Do Worms Have a Protective Role in *P. falciparum* Infection?

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Abstract

Malaria and intestinal helminths are sources of significant morbidity worldwide. Given the nature of shared endemicity, these diseases often co-exist in the same populations. Therefore, much attention is now being given to the interaction between helminths and *Plasmodium* in the situation of co-infection. Existing evidence is consistent with the hypothesis that helminths are associated with continued and possibly increased incidence of malaria infection. However, data from some recent clinical fieldwork suggest protection from cerebral malaria in the setting of helminth co-infection. Nitric oxide, coupled with the immunoglobulin E (IgE) receptor, CD23, appears to be a crucial factor in preventing the development of cerebral malaria, thus improving chances for the survival of both host and parasite. In this work, we review literature on the subject of helminth and malaria co-infection, and offer a theoretical explanation of the helminth modulation of clinical malaria. In doing so, we advocate further research on this subject and also the need for a dual approach in global disease control intervention, which simultaneously targets both malaria and geohelminth infection.

Key Words: Helminth, cerebral malaria, nitric oxide, CD23, malaria severity, co-infection.

Introduction

It has been estimated that infectious and parasitic diseases contribute 25% of the global disease burden (1). Annually, malaria, caused by *Plasmodium falciparum*, is implicated in an estimated 1.5–2.7 million deaths, with 300–500 million cases worldwide and nearly 40% of mankind residing in endemic malarial zones (2). Overall, the global burden of malaria, expressed in disability-adjusted life years (DALYs), is estimated at 42,280,000 (3).

The DALYs for intestinal nematodes have been calculated at 4,600,000 (3). The major soil-transmitted helminths (*Ascaris*, hookworm and *Trichuris*), coupled with schistosomiasis, are responsible for more than 40% of the worldwide morbidity from all tropical infections, excluding malaria (3). Ascariasis is the most common helminth infection, with more than 1.2 billion cases annually (4). Both trichuriasis and hookworm infection account for 700–800 million global infections. In total, more than 2 billion people are infected with helminths (3).

The morbidity associated with helminth infections is significant, although under-appreciated. Hookworm is implicated as the causative factor in more than 50% of cases of iron deficiency anemia in Africa and Asia (5). Additionally, hookworm is a significant cause of short stature and neurological developmental delay in endemic regions. *Ascaris lumbricoides* is a well-known cause of malnutrition, intestinal obstruction, biliary colic and pancreatitis (6).

Both hookworm and malaria are significant causes of anemia in pregnant women. The prevalence of hookworm infection among reproductive age females in sub-Saharan Africa is estimated to be as high as 32% (7). In one study, malaria was shown to cause 40% of anemia in breast-feeding and pregnant Congolese females (8). The same report identified intestinal helminths as the cause of nearly 10% of anemia in gravid and nursing females in Lubumbashi, Congo (8). The burden of malaria in children is also quite significant. Repeated malaria infection and subsequent severe

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anemia is implicated in a majority of all malaria-related deaths of Africa children (9).

The combined burden of malaria and helminthiasis in pregnant women has its most marked effect on birth weight. *Plasmodium* and helminth co-infection results in lower birth weight than *Plasmodium* infection alone (10). The situation is more pronounced for primigravid mothers (10).

Malaria and soil-transmitted helminths (STH) are widely co-endemic and are largely a burden of the poor (Figs. 1 and 2; 4). Inadequate sanitation, open sewers, crowded living conditions, and lack of access to health care are contributing factors. Recently, there has been much research focusing on the interactions between helminth and malaria infections in the same host. Preliminary data suggest a relationship between helminth infection and malaria incidence in addition to helminth-associated reduction in the severity of *Plasmodium* infection. This review will discuss the relationships between STH and malaria, with a focus on epidemiology, clinical manifestations, and molecular and immunologic factors of helminth suppression of malaria disease.

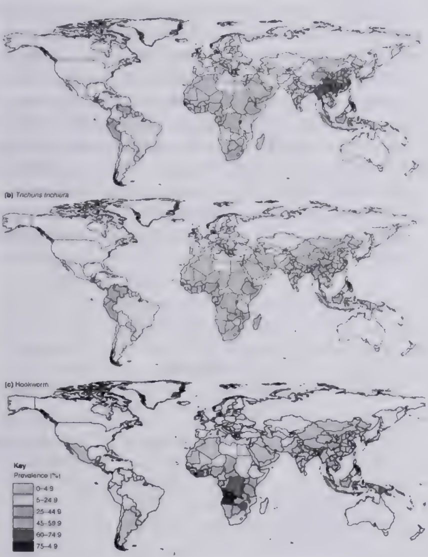

Fig. 1. Global distribution of intestinal helminths: *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm. White areas represent no endemicity.

Reproduced with permission from De Silva NR, Brooker S, Hotez PJ et al. Soil-transmitted helminth infections: updating the global picture. Trends Parasitol 2003; 19(12):547–551. From Elsevier-data obtained from http://www.fic.nih.gov/dcpp/dcp2.html (4)

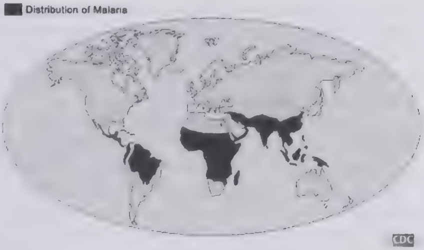

Fig. 2. Global distribution of malaria: all species. Reproduced from CDC website-http://www.cdc.gov/malaria/distribution_epi/distribution.htm

IgE = immunoglobulin E; NO = nitric oxide; TNF = tumor necrosis factor.

STH and the Incidence of Malaria

An early analysis relating the correlation between geohelminths and malaria was conducted by Murray et al. in the late 1970s. This group, studying children in Anjouan, an island in the Indian Ocean, noted a relative absence of malaria in patients with heavy *Ascaris lumbricoides* infection (11). The study population had a peculiar syndrome of localized forehead edema, bilateral painless enlargement of the parotids, and relative absence of *Plasmodium* infection (11). This syndrome was not present in ethnically similar children of the neighboring island, Grand Comore. The investigators noted that the chief difference in these populations was that the Anjouan group was heavily infected with *Ascaris*, while that of Grand Comore was relatively free of roundworms (11). In a subsequent study, the same research group treated the Anjouan patient population for *Ascaris* infection and noted a resolution of the syndrome, but a dramatic rise in the incidence of malaria (12). At the time, it was postulated that nutritional consequences of severe ascariasis led to malaria suppression in order to maintain host survival (12).

Later studies examining the relative effect of geohelminths on the incidence of *Plasmodium* infection have not supported the findings of Murray et al. Data from Africa point to a positive correlation between helminths and *Plasmodium* (13). Tshikuka et al. demonstrated that among their study group of patients, *Plasmodium* and *A. lumbricoides* caused the most frequent double infection, with a significant positive association between these two parasites (13). *Ascaris* has also been shown to impact mixed *Plasmodium* species infections. Contemporaneous and successive *vivax* and *falciparum* infections have been positively correlated with *A. lumbricoides* infection, suggesting an increased tolerance of human hosts to different *Plasmodium* species in the setting of helminth co-infection (14).

Nacher et al. conducted a study of 731 ethnically homogenous villagers in a low-transmission malarial zone of Thailand in an attempt to ascertain the incidence of malaria in helminth infections (15). In contrast to Murray's findings, this study showed an increased likelihood of *falciparum* malaria in patients with helminths (15). This increase in *falciparum* malaria was not related to the intensity of helminth infection, as all patients were asymptomatic with no massive infection of helminths. Rather, it was observed that the number of helminth species infecting the host played a role in the incidence of malaria. Patients with three or more helminth species were found to have the greatest risk of developing clinical *falciparum* malaria, defined as presence of malaria symptoms with a positive malaria slide (15). When adjusted for gender, age, and intestinal protozoa, the results held.

Shapiro et al. performed an epidemiological survey of helminth infections and their relationship to malaria in Uganda, utilizing a slightly different study design. They surveyed ethnically homogenous populations, in a low transmission zone, with similar rates of helminth infection (16) The survey was of 4 villages in Kabale district, Uganda. All 4 villages had similar rates of helminth infection. This study, contrary to Nacher's findings, found no increased susceptibility to clinical malaria in patients with helminth infection (16).

At present, the role of helminths in the incidence of *Plasmodium* infection is still unclear, although a significant relationship appears plausible. Numerous studies have shown a positive correlation between helminth infection and malaria, as well as an increased incidence of *Plasmodium* infection in the setting of STH infection. However, data have also been presented showing no correlation between malaria infection and helminth disease. The relationship is probably influenced by factors such as the number of helminth species and intensity of helminth infection, genetics, and other, undetermined factors. Expanded studies, spanning wider geographic locations and larger study populations and aimed specifically at understanding the epidemiology of helminth and malaria co-infection, are still required.

Geohelminths, Cerebral Malaria, and Acute Renal Failure

Severe complications of malaria include cerebral malaria, acute renal failure, jaundice, and profound anemia. While the role of geohelminths in the incidence of malaria infection is somewhat controversial, STH infections appear to have a protective role in the severity of malarial disease (Table 1; 17). Prospective, case-controlled clinical studies show that helminth-infected subjects are less likely to develop *Plasmodium*-associated acute renal failure and jaundice (17). Work done on murine models has pointed to diminished susceptibility to cerebral malaria after inoculation with helminths (18).

Reports from Thailand indicate a protective effect of *A. lumbricoides* against cerebral malaria (19). The protection against cerebral malaria appears to be related to the intensity of *Ascaris* infection. In their Thai study, Nacher et al. report a protection against cerebral malaria of between 40% (in mild *Ascaris* infection) and 75% (in intermediate *Ascaris* infection) (19). Interestingly, helminth-infected patients with cerebral malaria have a higher schizont/leukocyte ratio in peripheral blood when compared to controls (20). Given that schizonts typically reflect sequestered parasite burden, this finding suggests that higher *Plasmodium* parasite biomass is required to induce cerebral malaria in geohelminth-infected persons (20). Additionally, protection appears greatest in ascariasis. In comparison with other intestinal helminths, *A. lumbricoides* infection has been associated with the most significant reduction in susceptibility to cerebral malaria (19, 20). However, this observation may reflect an artifact of diagnosis, as *Ascaris* infection is typically easier to detect than that of other species, such as *Strongyloides* (20).

TABLE 1

Geohelminth Co-infection and Protection from P. falciparum-*induced Acute Renal Failure*

	Helminth Infection n (%)	**No Helminth Infection n (%)**
Patients with Acute Renal Failure	6 (6%)	16 (19%)
Controls	89 (94%)	68 (81%)

Adjusted odds ratio (95% CI) of 0.16 (0.03–0.85), p value 0.03

Reproduced with permission from Nacher M, Singhasivanon P, Silachamroon U, et al. Helminth infections are associated with protection from malaria-related acute renal failure and jaundice in Thailand. Am J Trop Med Hyg 2001; 65(6):834–836 (17).

Immunomodulation of *Plasmodium* Infection by Geohelminths: the Role of Nitric Oxide

Increasingly, research has focused on the causative factors of varying severity of malaria in hosts with geohelminth disease. This work has examined the controversial and still debatable effect of nitric oxide (NO). Several explanations have been offered with regard to the relationship of NO, helminths, and malaria. The literature has offered opposing and at times contradictory correlations between NO and the severity of malaria. Some studies have suggested a protective role of NO by showing urine NO excretion and plasma NO levels inversely related to disease severity (21). The highest levels of NO are found in subclinical infection and the lowest concentrations detected in cerebral malaria (21). Furthermore, another study from East Africa has shown that a nitric oxide synthase (NOS) genetic polymorphism is associated with elevated NO production and subsequent protection from cerebral malaria in children (22).

In contrast, NO has also been described as a pathogenic factor related to expression of clinical disease. Yaman et al. have reported that NO level is positively correlated with the intensity of *Plasmodium*-induced coma, as defined by the Blantyre Coma Scale (23). Median levels of reactive nitrogen intermediates are higher in children with deeper coma than those with lighter coma (23). Additionally, patients with clinical *falciparum* malaria and co-infected with geohelminths have increased anemia and decreased reticulocyte counts, when compared to controls (Table 2; 24). The mechanism of this phenomenon has been postulated to be NO-induced suppression of bone marrow erythropoiesis (24).

Clark et al. have theorized that inflammatory cytokines inducing NO production are responsible for cerebral malaria (25). Excessive production of tumor necrosis factor (TNF) and other inflammatory cytokines has been implicated in clinical severity of malaria (26). Clark et al. suggest that parasite sequestration results in increased endothelial synthesis of NO (25). This NO subsequently diffuses across the blood-brain barrier, resulting in an acute increase in intracranial pressure as well as disruption of the neuronal synapses (25).

TABLE 2

Differences in Mean Hemoglobin Concentration Between Helminth-Infected and Non-infected Patients in Mild and Cerebral Malaria

Mean Hemoglobin Concentration g/dL (± SD) [number of patients] Helminth Infection	No Helminth Infection	*Adjusted p Value
	(Mild Malaria)	
11 ± (2.5) [89]	12.2 ± (2.7) [91]	0.005
	(Cerebral Malaria)	
10.1 ± (3) [47]	11.2 ± (2.4) [64]	0.02

Adjustments for age, sex, ethnicity, mean corpuscular volume, parasitemia, symptom duration and nutritional status.

Reproduced with permission from Nacher M, Singhasivanon P, Gay F, et al. Association of helminth infection with decreased reticulocyte counts and hemoglobin concentration in Thai *falciparum* malaria. Am J Trop Med Hyg 2001; 65(4): 335-337 (24).

CD23, TNF-α, NO and Cerebral Malaria

In order to explain the apparent contradictions in the literature regarding elevated NO, malaria, and geohelminths, a more complicated theory has been offered involving the IgE cellular receptor, CD23. IgE binding proteins are divided into high- and low-affinity receptor types (27). CD23 is a low-affinity IgE receptor found on a variety of blood cells, including macrophages, monocytes, eosinophils, and B-lymphocytes. This receptor, when bound by a ligand such as IgE, triggers an elaborate intracellular response resulting in elevated endogenous NO levels (28).

CD23 also undergoes autoproteolytic cleavage and releases a soluble fragment, sCD23, which retains some capacity to bind IgE (29). sCD23 has pleiotropic functions, including potent stimulation of the production of the pro-inflammatory cytokine, TNF-α (30). The role of TNF-α in the pathogenesis of cerebral malaria is still unclear. However, there is some evidence suggesting that TNF-α may play a significant part in the development of cerebral and other severe forms of malaria. TNF-α levels have been correlated with severe malaria, defined by modified World Health Organization (WHO) criteria (31). Levels of this cytokine were noted to be elevated in children with cerebral malaria-related deep coma (32). Additionally, animal models have shown increased TNF-α in the brain of mice with fatal cerebral malaria (33).

IgE binding with CD23 reduces autoproteolytic cleavage to the soluble form, thereby reducing the levels of sCD23 and subsequently TNF-α production as well (27). Helminths are widely known to induce a strong IgE response. In helminth-infected hosts, the Th2 response elevates IgE concentrations with subsequent reduction of sCD23 expression (34, 35). As highlighted above, the increased IgE can activate monocyte populations by engaging CD23 receptors and thus stimulating NO production. This increased NO can subsequently play a role in down-modulating cerebral malaria.

Multivariate analysis demonstrates that the protective role of elevated NO in cerebral malaria inversely correlates with sCD23 levels (34). Increased concentration of NO is protective against cerebral malaria when sCD23 is low and pathogenic when sCD23 levels are elevated (34). Presumably, the mechanism for this finding is that low sCD23 levels result in diminished TNF-α production and thereby provide an additional mechanism for reduced incidence of cerebral malaria. The role of NO in the development of cerebral malaria in helminth co-infection is still controversial. Some investigators suggest a protective role while others observe a pathogenic mechanism. We suggest that, although NO appears to have some protective effect against cerebral malaria, it is actually a yet unquantified combination of NO, sCD23, and TNF-a that defines the degree of pathogenicity of cerebral malaria (Fig. 3).

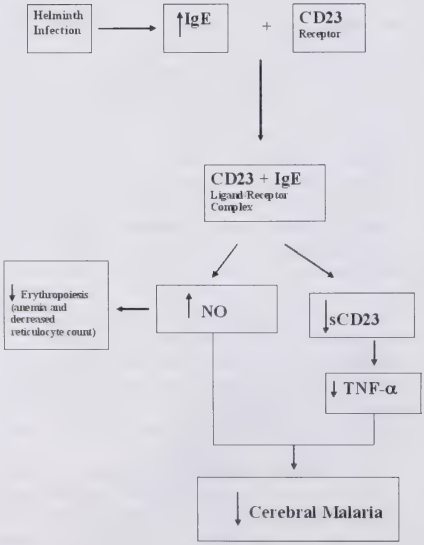
Helminth Infection
↑IgE
+
CD23 Receptor
CD23 + IgE Ligand/Receptor Complex
↓ Erythropoiesis (anemia and decreased reticulocyte count)
↑ NO
↓sCD23
↓ TNF-α
↓ Cerebral Malaria

Fig. 3. Helminth modulation of *Plasmodium* infection.

TNF = tumor necrosis factor; IFN = interferon.

Geohelminths and Malaria: The Th1/Th2 Perspective

An additional explanation for the apparent geohelminth-related clinical findings in *falciparum* malaria can be attributed to the thyroid hormone 1/thyroid hormone 2 (Th1/Th2) immune response. Infection with *falciparum* malaria is known to stimulate the Th1, pro-inflammatory immune response (36). This immune response is characterized by the release of TNF-α and interferon-g (IFN-γ). We have previously discussed the pathogenic potential of the Th1 cytokine, TNF-α, in cerebral malaria. The Th1 process, however, also has protective functions in clinical malaria, resulting from the production of IFN-γ. In experimental models, IFN-γ aids in elimination of *P. falciparum*-infected hepatocytes and hepatic schizonts within cells (37). Additionally, IFN-γ limits the initial phases of parasite replication (37). In human hosts, IFN-γ arrests the blood stage of malaria infection (37). Thus an early Th1 immune response is credited with the suppression of the blood and liver stages of the parasite life cycle. The Th1 immune response appears to be protective in the blood and liver stages but pathogenic in cerebral malaria.

The Th1 response is downregulated in the presence of the Th2 immune response. Helminth infection is a well-known stimulant of the production of IgE and the Th2 cytokine, TGF-β (38). We suggest that in malaria-geohelminth co-infection, the Th2 cytokine response possibly predominates, resulting in down-modulation of the Th1 cytokines (38). The TGF-β inhibition of IFN-γ subsequently prevents the IFN-γ protective effects in the blood and liver stages of malaria infection (38). This phenomenon could explain the worsening of anemia in geohelminth-malaria co-infection. Under the influence of Th2 cytokines, Th1-stimulated production of TNF-α, a factor implicated in the pathogenesis of cerebral malaria, is also reduced. The resultant advantageous effect is protection against cerebral malaria. Thus, the helminth-induced Th2 response appears protective with regard to cerebral malaria, but pathogenic by worsening anemia (Fig. 4).

Geohelminth and Malaria Co-infection: A "Precarious Balance"?

One recent review has suggested that helminth infection may worsen the outcome of clinical malaria infection (39). We believe that helminth co-infection is not entirely deleterious, but also protective from some potentially lethal forms of *P. falciparum* infection. In presenting this argument,

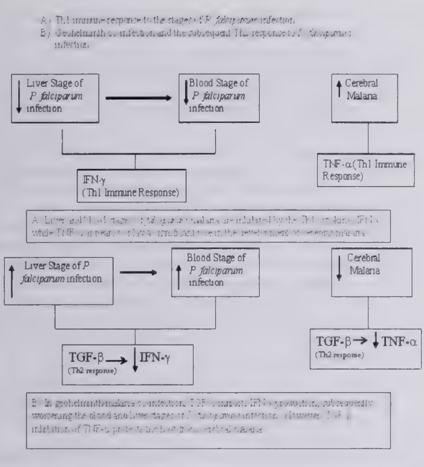
A) Th1 immune response to the stages of P. falciparum infection.
B) Geohelminth co-infection and the subsequent Th2 response to P. falciparum infection.
Liver Stage of P falciparum infection
Blood Stage of P falciparum infection
Cerebral Malaria
IFN-γ (Th1 Immune Response)
TNF-α(Th1 Immune Response)
Liver Stage of P falciparum infection
Blood Stage of P falciparum infection
Cerebral Malaria
TGF-β → IFN-γ
(Th2 response)
TGF-β → TNF-α
(Th2 response)

Fig. 4. Geohelminth and malaria co-infection: The Th1/Th2 immune response.

(A) Th1 immune response to the stages of *P. falciparum* infection. **(B)** Geohelminth co-infection and the subsequent Th2 response to *P. falciparum* infection.

we agree that helminth co-infection worsens some clinical features of malaria such as anemia. It is also possible that helminth infection may cause an increase in the incidence of clinical malaria. However, helminth infection is probably protective with regard to some severe forms of the disease, such as cerebral malaria.

Cerebral malaria presents a very high risk of mortality. Over time, selection has favored geohelminths that have adapted to confer host protection from cerebral malaria by immunomodulating *Plasmodium* infection, thereby resulting in a precarious balance of helminth-malaria co-infection. Helminths allow for *Plasmodium* infection to continue, but decrease host mortality from complications such as cerebral malaria (Fig. 5). The mechanism for this appears to be mediated by NO, sCD23, and the Th1/Th2 cytokines, TNF-α, IFN-γ, and TGF-β. With regard to *Plasmodium* infection, increased NO has deleterious effects on the host, but in the setting of helminth co-infection and subsequent low sCD23 and TNF-a, nitric oxide also protects the host from cerebral malaria (34). Helminth infection also up-regulates the Th2 cytokine response, causing subsequent down-modulation of the Th1 immune pathway and ultimately resulting in protection from cerebral malaria. These explanations suggest that helminths confer an increase in host protection and thus ensure continuation of dual parasitism.

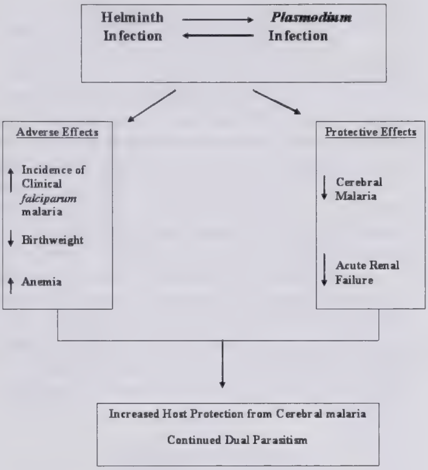
Helminth Infection
Plasmodium Infection
Adverse Effects
Incidence of Clinical falciparum malaria
Birthweight
Anemia
Protective Effects
Cerebral Malaria
Acute Renal Failure
Increased Host Protection from Cerebral malaria
Continued Dual Parasitism

Fig. 5. Malaria and helminth co-infection in humans: a precarious balance?

Implications for Current Intervention Programs

From the data presented above, we can conclude that intestinal helminth infections have an effect on the clinical expression of malaria. However, the direction and magnitude of this effect are not clear. If intestinal helminthiasis does provide protection from cerebral malaria, de-worming programs may result in the increased incidence of cerebral and other severe forms of malaria.

Under the circumstances, it would be good to examine this question rigorously in the epidemiologic context of highly endemic malaria and intestinal helminths prior to the implementation of large-scale de-worming programs. We suggest that prospective, carefully controlled clinical studies be conducted in villages with heavy burdens of malaria and intestinal helminths. After collection of baseline data (intestinal helminth burden, malaria parasitemia and anemia) all persons in randomly selected villages could receive albendazole; control villagers would receive placebo. Both populations would be monitored for clinical malaria, anemia and other clinical sequelae of malaria infection. Under this experimental model, the population receiving antihelminthic drugs should, under our hypothesis, experience a statistically significant rise in the incidence of severe and cerebral malaria. However, we recognize the ethical need for treating patients once symptoms of clinical malaria present. Thus, observing patients for the development of cerebral malaria is not possible. However, given the data showing lowered hemoglobin levels in helminth and malaria co-infection, patients treated with albendazole should have statistically significant elevation in hemoglobin when compared to controls. This type of study should further the understanding of geohelminth and malaria co-infection and shed significant light on the ecological balance between these two diseases.

Additionally, if helminth infection confers protection against the development of severe malaria, current global control programs should be modified to treat both diseases simultaneously. For example, de-worming programs could be combined with the distribution of insecticide-treated bed nets.

Acknowledgements

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A Randomized, Placebo-Controlled Trial of a Single Dose of Tropisetron for the Prevention of Vomiting after Strabismus Surgery in Children

Zeynep Tosun, M.D.[1], Aynur Akin, M.D.[1], Hakki Dogan, M.D.[2], and Adem Boyaci, M.D.[3]

Abstract

Purpose: This study evaluates the effect of different doses of tropisetron to prevent postoperative vomiting, which frequently occurs in children following strabismus surgery.

Methods: One hundred twenty-five American Society of Anestesiologists' classification (ASA) I–II group patients 2–12 years of age were randomized to this prospective, single-blind, placebo-controlled clinical study. Patients were placed in groups of 5 and did not receive any premedication. The first group received placebo, and the 2nd, 3rd, 4th, and 5th groups received 0.5 mg/m^2, 1 mg/m^2, 1.5 mg/m^2, and 2 mg/m^2 of tropisetron, respectively, following anesthesia induction. The same anesthetic technique and analgesia were used for all groups. The patients were examined for the presence of vomiting and for any complaints and side effects at 2, 6, and 24 hours after surgery.

Results: The incidence of postoperative vomiting (POV) was statistically more significant in the placebo group at 2, 6 and 24 hours, when compared to the study groups ($p< 0.001$), but there was no significant difference among tropisetron groups at 6–24 hours ($p>0.05$). There was no significant difference in terms of the incidence of POV among the study groups (16%, 16%, 24%, 20% respectively) at all periods ($p>0.05$). The number of patients with POV score of 3 was 10 in the placebo group, while it was 1, 2, 0 and 1 in the 2nd, 3rd, 4th, and 5th groups, respectively ($p<0.01$).

Conclusions: Tropisetron (0.5, 1.0, 1.5 and 2.0 mg/m^2) decreased the incidence and severity of POV following strabismus surgery in children. All of the doses seemed to be equally effective. There was no difference in POV control between placebo and any of the doses of the tropisetron after six hours. So we suggest that 0.5 mg/m^2 single-dose tropisetron is enough for preventing POV following strabismus surgery in children.

Key Words: Postoperative vomiting, strabismus surgery, tropisetron, children.

Introduction

Postoperative nausea and vomiting (PONV) after strabismus surgery is a major problem in the pediatric population. PONV is still being experienced by 41–88% of patients following strabismus surgery when antiemetic prophylactics are not administered (1). The etiology of postoperative vomiting is multifactorial and complex. It is related to the surgery and the drugs used during anesthesia (2). The high incidence of PONV is attributed to the manipulation of the eyeball and release of various neurotransmitters in the chemoreceptor trigger zone through the oculoemetic reflex (3), postoperative distortion of vision (4), postoperative pain, and use of opioid analgesia in the perioperative period (2).

Not only is POV a disturbing situation for the patient, but it is also a complication causing aspiration, delayed wound healing, increased hemorrhage and increased hospitalization time (5). The new generation of antiemetic agents, called 5-HT$_3$ receptor antagonists (ondansetron, granisetron, ramosetron, dolasetron), are superior to conventional antiemetics for the prevention and treatment of PONV (5). Besides this, a combination of these agents with dexamethasone or droperidol was found to be superior in antiemetic effect after strabismus surgery in children (6–8). Tropisetron, 5-HT$_3$ receptor antagonist with a long elimination half-life, seems to be more effective with one-dose application than the other agents for the prevention and treatment of PONV (9). Yet to the best of our knowledge, tropisetron has never been used in that specific surgical situation. The aim of this study was to evaluate the effectiveness of prophylactic tropisetron in a dose-response relation in children undergoing strabismus surgery.

Methods

Following permission from the local ethics committee, informed consent was obtained from the parents. One hundred twenty-five ASA I–II

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group patients between 2 and 12 years of age with strabismus were randomized for this prospective single-blind, placebo-controlled study. Patients using any other medication (especially those having an antiemetic effect, such as corticosteroids) and patients who were developmentally delayed were not included in the study. For all patients, we noted the age, gender, body weight, body surface area (BSA), number of eyes and extraocular muscles operated on, the amount of crystalloid given intraoperatively, the agent used for the induction, duration of anesthesia and extubation, recovery time and the number of vomiting attacks. We also noted the number of patients receiving rescue antiemetic. BSA was calculated by the formula offered by Vaughan and Litt (10). Patients were not premedicated, and they fasted for at least 6 hours before the surgery. Heart rhythm (with ECG), non-invasive blood pressure, peripheral oxygen saturation and $EtCO_2$ were monitored.

Anesthesia induction was achieved with 6 mg/kg thiopental (T) or 8% sevoflurane (S) in 50% N_2O–O_2. Tracheal intubation was carried out after an injection of 0.1 mg/kg of vecuronium. Nasogastric decompression was not done in any patient and i.v. 1 μg/kg fentanyl was given as an additional analgesic to all patients. Two percent sevoflurane in 50% N_2O–O_2 was used for the maintenance of anesthesia. During induction, the first group received placebo (5 mL of physiologic saline [PS]), the second group received 0.5 mg/m^2 of tropisetron, the third 1 mg/m^2 of tropisetron, the fourth 1.5 mg/m^2 of tropisetron and the fifth 2 mg/m^2 of tropisetron (max BSA 1.2 m^2) (diluted with 5 mL of PS). Intraoperative i.v. hydration was achieved with 1/3 PS and was arranged to complete the body fluid deficit during the first hour and to continue as maintenance according to the body weight thereafter.

Neuromuscular block was reversed with 0.01 mg/kg atropine and 0.03–0.05 mg/kg neostigmine at the end of surgery. The time for the patients to reach a score of 9 on Aldrete's postanesthetic recovery assessment (11) after extubation was recorded as recovery time. Patients were followed in the recovery room for the first 2 hours and were assessed for POV, complaints and side effects for 24 hours. Postoperatively, all episodes of retching and vomiting were recorded by nursing staff who did not know which treatment each patient had received. Retching was assessed as vomiting, and POV was scored as follows; one = no vomiting, two = vomiting once within 30 minutes, three = vomiting twice or more within 30 minutes. Patients with a score of three were given 0.15 mg/kg of metoclopramide as a rescue antiemetic. Complaints and side effects of the groups in Table 1 were also recorded by nursing staff who did not know which treatment each patient had received at 2, 6, and 24 hours. Postoperative pain was treated with ibuprofen (10 mg/kg) p.o. No alternative forms of analgesic were administered to the patients.

Analysis of variance (ANOVA) with post-hoc test (Bonferroni correction) was used for the statistical analysis of the difference between the groups with respect to age, body weight, BSA, duration of anesthesia and extubation, recovery time, amount of crystalloid given intraoperatively and the number of vomiting attacks. The statistical analysis of the difference among the groups with respect to sex, the agent used for the induction and the incidence of POV was done with chi square test; with respect to the number of operated eyes and extraocular muscles, the analysis was done with the Kruskal-Wallis test. The number of patients with a POV score of three and the number of patients receiving rescue antiemetic for complaints and side effects was analyzed with Fisher's exact chi-square test. A p value of less than 0.05 was assessed as statistically significant.

Results

Demographic and clinical data for all groups are presented in Table 2. Each group consisted of

TABLE 1

Incidence of Complaint and Side Effects of the Groups

Complaints and side effects No. (%)	**Placebo (n=25)**	**Tropisetron Groups (mg/m^2) (n=25)**			
		Group I	**Group II**	**Group III**	**Group IV**
Agitation	5 (20)	4 (16)	6 (24)	4 (16)	5 (20)
Pain (headache, sore throat, abdominal, eye)	5 (20)	4 (16)	7 (28)	9 (36)	8 (32)
Drowsiness	1 (4)	0 (0)	0 (0)	1 (4)	2 (8)
Others (fever, cough, itching, giddiness, anxiety)	1 (4)	0 (0)	0 (0)	2 (8)	3 (12)

No significant differences among the groups. Data are presented as ( )%.

TABLE 2
Demographic and Clinical Data

	Group I (Placebo) (n= 25)	Tropisetron Groups (mg/m^2) (n= 25)			
		0.5	1	1.5	2
Age (yr)	6.92±3.10	5.47±2.7	6.45±2.2	6.35±2.2	6.45±2.6
Sex (M/F)	10/15	14/11	16/9	12/13	12/13
Weight (kg)	24.16±10.07	19.8±9.9	22.2±5.1	21.7±5.2	22.3±7.7
BSA (m^2)	0.84±0.18	0.74±0.16	0.82±0.11	0.81±0.1	0.79±0.2
Induction agent (S/T)	11/14	10/15	12/13	14/11	9/16
No. of operated eye					
Median (min-max)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)
No. of operated muscles					
Median (min-max)	2 (1–4)	2 (1–4)	2 (1–2)	2 (1–3)	2 (1–3)
Intraoperative fluid (mL/kg)	19.3±3.07	19.32±3.4	19.18±3.9	19.36±1.7	20.16± 4.2
Duration of anesthesia (min)	71.04±25.5	72.8±32.2	64.2±28.8	73.6±29.1	72.4± 30.2
Duration of extübation (min)	4.28±3.17	5.48±3.4	4.63±3.23	4.8±1.4	4.9± 1.99
Recovery time (min)	5.7±5.03	5.44±4.52	4.44± 2.56	5.9±5.32	4.97±4.27

BSA = body surface area

25 patients. In this study, we detected no statistically significant differences among the groups with respect to age, sex, body weight, BSA, the agent used for induction, duration of anesthesia, duration of extubation, the number of eyes and muscles operated on and the amount of crystalloid given intraoperatively, and recovery time (p>0.05).

Although the incidence of POV was statistically more significant in the placebo group at 2 and 6 hours when compared to the study groups (p<0.001), there was no significant difference among the groups at 6–24 hours (p>0.05). The incidence of POV was significantly less in the study groups as compared to the placebo group when the whole observation period (0–24 hours) was considered (p=0.001). There was no significant difference in terms of the incidence of POV among the study groups at all periods (p>0.05). The number of patients with POV score of 3 was 10 in the placebo group, but it was 1, 2, 0 and 1 in the 2nd, 3rd, 4th, and 5th groups, respectively (Fisher exact chi-square test p<0.01).

The number of patients who needed rescue antiemetic was 10 in the placebo group, but it was significantly lower (1, 2, 0, and 1, respectively) in the study groups (chi-square test, p<0.001) (Table 3).

There was no difference among the groups in terms of the incidence of complaint and side effects (Table 1).

Study power analysis was determined in groups 2, 3, 4, and 5 as 91%, 91%, 74%, and 84%, respectively (ß= 0.20, α= 0.05). The incidence of POV in the placebo group (60%) descreased 16%, 16%, 24%, and 20% in the study groups (the analysis used version 2.1 of PS Power and sample size calculations). Confidence intervals were calculated for the incidence of POV of 0–24 hours (Table 4).

Discussion

The present study demonstrated that 0.5 mg/m^2 of tropisetron was as effective as higher doses in reducing the incidence of POV. Tropisetron significantly reduced the incidence of POV from 60% to 16–24% in this pediatric strabismus surgery patient population (p= 0.001). Tropisetron also reduced the frequency of vomiting: 40% in the placebo group vomiting more than two times, compared with 0–8% in the study groups.

In the literature, there are only a few clinical studies for the use of tropisetron on POV in children in specific surgical situations (12–15). These specific situations were tonsillectomy and adenoidectomy, and the dose was 0.1 mg/kg (12–14). Only Jensen et al. used 0.2 mg/kg tropisetron to reduce PONV associated with pediatric tonsillectomy (15).

Kranke et al. (16) surveyed studies investigating the efficacy of tropisetron vs. placebo to prevent postoperative nausea and vomiting, separately or together (MEDLINE, EMBASE, Cochrane-Library, reference lists; last update December 2001). It was reported that there was no clear evidence for a dose response between 2 and 5 mg i.v. for adults. For children a dose of 0.1 mg/kg of body weight is effective. These results support our results, since low doses were as effective as higher doses in our study. Alon et al., in a study investigating the effectiveness of different doses of tropisetron (0.5, 2

TABLE 3

Incidence and Severity of Postoperative Vomiting (POV)

POV Incidence No. (%)	Group I (Placebo) (n=25)	Tropisetron Groups (n=25) Group II	Group III	Group IV	Group V
0–2 h	15 (60)*	2 (8)	4 (16)	4 (16)	4 (16)
2–6 h	10 (40)*	2 (8)	1 (4)	2 (8)	0 (0)
6–24 h	1 (4)	0 (0)	0 (0)	1 (4)	1 (4)
0–24 h	15 (60)*	4 (16)	4 (16)	6 (24)	5 (20)
No. of patients with POV score of 3	10 (40)*	1 (4)	2 (8)	0 (0)	1 (4)
Emetic episodes per patient (mean±SD)	1.4±1.38*	0.2±0.5	0.28±0.74	0.28±0.54	0.24±0.52
No. of patients who needed antiemetic rescue	10 (40)*	1 (4)	2 (8)	0 (0)	1 (4)

*p<0.01 compared with study groups. No significant differences among the study groups.
Data are presented as ( )%.

TABLE 4

95% CI of Incidence of POV (0–24 h)

Tropisetron Groups	Incidence of POV (95% CI)
Group I (Placebo)	0.60 (0.47–1.00)
Group II (0.5 mg/m²)	0.16 (0.07–0.23)
Group III (1 mg/m²)	0.16 (0.07–0.23)
Group IV (1.5 mg/m²)	0.24 (0.13–0.37)
Group V (2 mg/m²)	0.20 (0.10–0.30)

POV = postoperative vomiting
CI = confidence intervals

and 5 mg) in a group of 1,513 adult patients, reported that all three doses seemed to be equally effective. However, 2 mg was reported to be the ideal dose, since nausea was least with this level (17). Only vomiting was evaluated in the present study, since nausea could not be measured accurately in young children. Alon's results also support our results. Gregory and Ettinger (18) had reported that interactions at the receptor level, and not plasma pharmacokinetics, were more important for defining the efficacy of 5-HT_3 receptor antagonists. So it may be that low doses of tropisetron are as effective as higher doses.

The present study also demonstrated that there was no difference between placebo control and any of the doses of tropisetron after six hours. The incidence of POV had peak values in the period 0–2 h. While the incidence of vomiting in the early postoperative period was 60% at 0–2 h, this incidence decreased 40% at 2–6 h in the placebo group. POV incidence was 8–16% at 0–2 h in the study groups, but it was 0–8% at 2–6 h. A very small percentage of the patients vomited in the 6–24 h period: 4% (1/ 25) of the patients in the placebo group and 0%, 0%, 4%, 4% of the patients in the tropisetron groups. Jensen et al. (15) reported peak values for both frequency and incidence of vomiting in the 4–8 h period and suggest that they may coincide with the first oral intake of fluids. They also reported that a very small percentage of the patients vomited for the first time in the 12–24 hour period: 2.9% (1/35) of the patients in the tropisetron group and 11.1% (4/36) of the patients in the placebo group, respectively. Jensen suggests that postponement of the time for first oral intake might reduce vomiting. Our routine procedure is to attempt to initiate oral fluids 5 h after surgery.

Elimination half-life of tropisetron is longer than that of other $5HT_3$ receptor antagonists (e.g., granisetron 3.1 h, ondansetron 3.2–3.7h, ramosetron 5.8 h); elimination half-life of tropisetron was reported to be as short as 8 hours in patients with a high metabolic rate (such as children) and as long as 30–42 hours in patients with a low metabolic rate (19). This long half-life permits one dose of tropisetron to be enough for the prevention of POV after strabismus surgery.

In a study on the pharmacokinetics of tropisetron by Gaedicke et al., because of a smaller volume of distribution, children showed a higher C_{max}/dose and higher area under curve (AUC) dose than adults did. Because of its age-dependent volume of distribution, it is recommended that tropisetron be administered once a day according to the BSA in children below 10 years of age (20). (We used tropisetron according to the BSA.)

The incidence of POV in the placebo group of the present study (60%) was similar to those of Ang (12), Shende (6), Wagner (21) and Madan (22), but was less than those of the other studies in the literature (1, 23–25). In the present study, the incidence of severe POV (score = 3) in the first 24 hours was 40% in the placebo group, with an incidence of vomiting in the early postoperative period of 60%. Several factors probably contributed to POV equally across our tropisetron groups. But the results were not affected by the choice of anesthetic technique, since all groups received a standardized technique.

The incidence of POV in our tropisetron groups (16–24%) was similar to those of the previous studies (9, 12, 19, 22). Other 5-HT_3 inhibitors have been shown to reduce POV in pediatric strabismus surgery (1, 8, 21, 25). Fujii et al. (8) compared the efficacy of granisetron (40 μg/kg) plus droperidol (50 μg/kg) with each antiemetic alone for the prevention of vomiting after pediatric strabismus surgery. They reported that a complete (i.e., optimum) response 0–3 h after anesthesia was 80% with granisetron, 45% with droperidol and 98% with granisetron plus droperidol, and 3–24 h after anesthesia was 78%, 38% and 98%, respectively. Sadhasivam et al. (1) studied the dose response and antiemetic effectiveness of prophylactic ondansetron in the prevention of PONV in children undergoing strabismus repair. They reported that ondansetron at a dose of 75 μg/kg was as effective as 150 μg/kg in preventing PONV after strabismus repair in children. Wagner et al. (21) investigated the efficacy and safety of dolasetron for the prevention of emesis, comparing a single 0.35 mg/kg or fixed 12.5 mg dose with placebo in children undergoing strabismus surgery. They concluded that there was no statistical difference between the 0.35 mg/kg dose and the fixed 12.5 mg dose of dolasetron, with both reducing the incidence of POV. Fujii et al. (25) evaluated the efficacy and safety of a single dose of ramosetron at 1 of 3 different doses (3 μg/kg, 6 μg/kg, or 12 μg/kg) for preventing POV in children undergoing strabismus surgery. They reported that a 6 μ/kg dose of ramosetron was sufficient, but a 3 μg/kg dose was insufficient for preventing POV during the 0–48 hour period after anesthesia, in children undergoing strabismus surgery. Increasing the dose to 12 μg/kg of ramosetron provided no demonstrable additional benefit.

When complaints and side effects were considered, there was no significant difference among tropisetron groups. And tropisetron was found to be not different from placebo with respect to side effects in previous studies (9, 26, 27).

In conclusion, 0.5, 1, 1.5 and 2 mg/m^2 of tropisetron decreased the incidence and severity of POV following strabismus surgery in children. All of the doses seemed to be equally effective. There was no difference in POV between placebo and any of the doses of the tropisetron after six hours. So we suggest that 0.5 mg/m^2 single-dose tropisetron is enough to prevent POV following strabismus surgery in children.

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Tuberculous Peritonitis and Tuberculous Endometritis Diagnosed in the Same Patient by High Clinical Suspicion and a Minimally Invasive Approach

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Abstract

Tuberculous peritonitis and tuberculous endometritis are extremely rare entities in the Western world. In this article, we discuss a rare case of a 40-year-old Nigerian female presenting with abdominal pain, distension and secondary amenorrhea, and show that a high clinical suspicion combined with minimally invasive procedures can help physicians make the diagnosis, avoid extensive surgery, and rapidly initiate appropriate therapy.

Key Words: Tuberculous peritonitis, peritoneal tuberculosis, extrapulmonary tuberculosis, minimally invasive approach, tuberculous endometritis.

Case Report

A 40-YEAR-OLD NIGERIAN FEMALE presented complaining of increasing abdominal pain and distension over the preceding one and a half months. Upon further questioning, the patient stated that she had experienced night sweats, weight loss of 27 lb over the past three months, fevers and chills, with an intermittent minimally productive cough. She also reported symptoms of amenorrhea over the preceding six months, with scant vaginal spotting. The patient's medical history included iron deficiency anemia and her surgical history was significant for five terminations of pregnancy in Nigeria, as well as an appendectomy, which required a blood transfusion. The patient stated that she is monogamous and denied any history of sexually transmitted infections. However, her husband practices polygamy and the patient stated that she had been raped in Nigeria by several assailants. The patient also described the presence of multiple infections with candidal vaginitis over the past year, self-treated with over-the-counter medications.

Upon presentation, the patient was febrile (oral temperature: 39.7 C). Physical examination revealed a grossly distended abdomen with voluntary diffuse guarding and tenderness to light palpation. However, there was no rebound tenderness or organomegaly. Bowel sounds were present and normoactive, and there was no fluid wave or shifting dullness. Pelvic examination, conducted by the gynecology service, was unremarkable. Routine laboratory tests showed leukocytosis (12,700) with a left-shift (poly: 85%, lymph: 1%). A chest film was obtained and was negative. A computed tomography (CT) chest scan revealed bilateral apical scarring of lung parenchyma and multiple 1–5 mm nodules that were scattered diffusely throughout both lungs. CT scan of the abdomen using intravenous and oral contrast showed loculated fluid collections within the mesentery and omentum and thickened peritoneum (Fig.). A differential diagnosis of disseminated tuberculosis with tuberculous peritonitis versus peritoneal carcinomatosis from ovarian carcinoma was considered. Sputum acid-fast bacilli (AFB) smear showed numerous bacilli, confirmed as *Mycobacterium tuberculosis* by polymerase chain reaction (PCR). Tuberculin skin test showed 9 mm induration. A rapid HIV test returned positive, and was confirmed using western blot analysis. An HIV-1 RNA PCR quantitation

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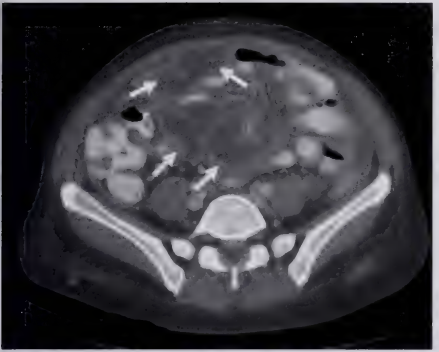

Figure. Computed tomography scan of the abdomen, using intravenous and oral contrast, showing loculated fluid collections within the mesentery and omentum (white arrows) and thickened peritoneum.

was obtained and indicated over 750,000 viral copies/mL. A lymphocyte subset showed a CD4+ T-lymphocyte count of 67 cells/μL. Malaria smear and serologies for hepatitis B and C, cytomegalovirus and toxoplasma were negative. CA-125 tumor marker was drawn and returned elevated (159 kU/mL). Ascites fluid, obtained by CT-guided paracentesis, was sent for chemistry, cytology and cytopathology studies and revealed an exudative fluid (serum-ascites albumin gradient: 0.5) with lymphocyte predominant leukocytosis (white blood cell count: 2,160, poly: 30%, lymph: 58%, mono: 12%) and no evidence of malignancy. *M. tuberculosis* PCR, AFB smear, and bacterial and fungal cultures were negative. Adenosine deaminase (ADA) level was 14.5 (normal 0.0–7.6). Endometrial samples obtained by dilatation and curettage were sent for cytopathologic and microbiologic analysis. Although cytopathology was limited due to sampling error, mycobacterial culture was returned with growth of *M. tuberculosis* complex.

A diagnosis of tuberculous peritonitis and tuberculous endometritis was made, given the extensive history and supporting laboratory results of this patient. Further questioning revealed that the patient's mother, with whom the patient had been in close contact, was reported to have died from tuberculosis. The patient was placed in respiratory isolation, and directly observed therapy (DOT) was started with a four-drug regimen of isoniazid, rifabutin, ethambutol, and pyrazinamide. Sputum culture was returned four weeks later with growth of *M. tuberculosis* complex sensitive to isoniazid, rifampin, rifabutin, ethambutol, pyrazinamide, and streptomycin. The patient began experiencing improvement in symptoms, and her CA-125 level decreased (36 kU/mL) two weeks after therapy was begun.

Discussion

Peritoneal tuberculosis (TB) is an exceptionally rare disease in the Western world. Nevertheless, its incidence has increased recently, and it accounts for 1.25% of all TB cases, and 6.1% of cases of extrapulmonary TB (1). It manifests as abdominal distension, ascites, fever, and weight loss. Serum level of CA-125 and ascites ADA level are frequently found to be elevated in patients with TB peritonitis (2).

Tuberculous endometritis is also a rare presentation of extrapulmonary TB. National TB surveillance data gathered by the Centers for Disease Control and Prevention indicate a genitourinary site of TB in only 1.8% of cases (1). The clinical manifestations of tuberculous endometritis may not be evident for years after initial infection. Most commonly, uterine TB presents with infertility (44%), pelvic pain (25%), vaginal bleeding (18%), amenorrhea (5%), vaginal discharge (4%) and postmenopausal bleeding (2%) (3). Laboratory results supporting the diagnosis are similar to those found with peritoneal TB, and include high erythrocyte sedimentation rate, falsely elevated CA-125 level, positive tuberculin skin test, and chest x-ray consistent with TB.

Endometrial TB infection generally results from reactivation of organisms from a previous distribution of tubercle bacilli during primary infection (4). There is also evidence to suggest that direct transmission between sexual partners can occur (5). It is possible that direct peritoneal involvement could have occurred from primary reactivation of TB in the endometrium secondarily transferring to the abdominal cavity via the fallopian tubes. Alternatively, concurrent reactivation of previous peritoneal seeding is also a likely etiology.

Considering that ovarian cancer presents with nonspecific signs and symptoms similar to those seen in these conditions, obtaining a definitive diagnosis without invasive intervention is often difficult. The standard for diagnosis of peritoneal tuberculosis infection is laparoscopic surgery with peritoneal biopsy (6), while definitive diagnosis of tuberculous endometritis relies upon successful endometrial biopsy with subsequent histological and microbiologic examination. Nevertheless, efficient use of a minimally invasive intervention (paracentesis) combined with PCR analysis of ascites fluid can potentially obviate the need for exploratory surgery. In this case, ascites fluid PCR was not helpful in our analysis. The lack of malignant cells and the presence of lymphocyte-predominant leukocytosis in ascites fluid, elevated ascites ADA levels, positive sputum PCR for *M. tuberculosis* and a strong clinical suspicion confirmed the diagnosis of TB peritonitis. Meanwhile, an endometrial biopsy specimen obtained via dilatation and curettage made possible a microbiological study that eventually grew mycobacteria, leading to successful recognition of tuberculous endometritis in this patient. Interestingly, the chest film taken of this patient was reported as negative without evidence of parenchymal disease. However, a CT scan of the chest, which is more sensitive in revealing chest pathology, was performed, given the high clinical suspicion of pulmonary involvement. It is probable that pulmonary involvement explained the sputum positivity that was noted in this patient. However, endobronchial TB could not be confirmed, due to lack of direct inspection of endobronchial mucosa and tissue sampling by bronchoscopy in our patient. It is important to maintain a high clinical suspicion for disseminated TB presenting since TB peritonitis and TB endometritis in patients with risk factors such as recent immigration from or travel to a country endemic for TB, close contact with TB-infected individuals, history of immunocompromise, confinement in prisons or institutions, and homelessness. Our patient's recent immigration from Nigeria, positive test for HIV, reactive tuberculin skin test, and close contact with an individual with TB made the diagnosis more likely than ovarian cancer, and allowed for minimal intervention combined with effective therapy.

The implications for management are important, given that the current management of ovarian carcinoma involves cytoreductive surgery followed by chemotherapy, whereas peritoneal TB is managed medically with DOT directed against *M. tuberculosis*. The response to treatment by patients with TB peritonitis and TB endometritis is usually rapid, and there is marked improvement in signs and symptoms as well as a rapid decline in serum levels of CA-125 (7). Our patient showed marked clinical improvement following anti-tuberculosis therapy. Despite her immunodeficient status and HIV positive serology, anti-retroviral therapy (ART) was deliberately delayed, to reduce the risk of immune reconstitution inflammatory syndrome (IRIS). ART was initiated following completion of anti-TB therapy. A follow-up CT examination of the abdomen nine months after therapy showed resolution of the patient's condition, which corresponded well to her clinical state.

In short, we found that a high clinical suspicion combined with minimally invasive testing is an effective way to diagnose tuberculous peritonitis, and that correct diagnosis can lead to effective therapy and a positive outcome.

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Ileosalpingeal Fistula:

An Unusual Complication of Crohn's Disease

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Abstract

Enterosalpingeal fistula is a rare complication of Crohn's disease. And it is rarely diagnosed pre-operatively. We describe two cases of enterosalpingeal fistula. Both cases were diagnosed during exploration and required en bloc resection of the small bowel and fallopian tube. Literature review yielded only one specific case report of ileosalpingeal fistula and two other cases described in a larger series. Management of ileosalpingeal fistula should include resection of the diseased bowel as well as removal of the affected fallopian tube.

Crohn's disease has an extremely wide spectrum of clinical manifestations. The hallmark of Crohn's disease is bowel inflammation with fistula or stricture formation. Organs commonly involved in fistula formation include the skin, small bowel, colon, and bladder. Rare fistula sites include the duodenum, stomach and gynecological structures such as the ovaries, fallopian tubes and vagina. We present two cases of Crohn's disease of the terminal ileum fistulizing to the fallopian tube. There is only one specific report of an ileosalpingeal fistula, although another author has described two additional cases in a large series of Crohn's fistulas.

Key Words: Crohn's disease, ileosalpingeal fistula, enterosalpingeal fistula.

Case 1

A 28-year-old African-American woman with complaints of vomiting, weight loss, fatigue and abdominal pain was diagnosed with Crohn's disease fourteen years previously. She underwent an exploration two years later for acute right lower quadrant pain. Although no intestinal resection was done at the time, her hospital course was complicated by an enterocutaneous fistula requiring a three-month hospitalization and total parenteral nutrition. The fistula eventually closed, and she remained well for two years. For the next eleven years, she had symptoms that were medically managed. She presented again in early 2005 with abnormal frequency of bowel movements and abdominal discomfort. The patient had been maintained on a medical regimen of prednisone, 6-mercaptopurine (6MP), mesalamine and ciprofloxacin. She had no other significant medical history and had never been pregnant; her menses began at age 12 and have been regular. Abdominal exam revealed only right lower quadrant tenderness to deep palpation.

The patient underwent colonoscopy, which revealed a stricture at the rectosigmoid as well as an adjacent ileal-rectal fistula. Biopsies of the fistulous tract revealed inflammation. A subsequent gastrograffin enema revealed multiple short fistulas between the rectosigmoid and ileum. Contrast from the ileum filled the colon in an antegrade fashion; it showed no mucosal abnormality in the right, transverse or left colon. The patient was taken to the operating room, where she underwent placement of bilateral ureteral catheters followed by laparotomy, during which a large pelvic mass involving the terminal ileum, rectosigmoid, bladder and the fallopian tube was found. *En bloc* resection of the ileocolic region, right fallopian tube and rectosigmoid, and closure of a bladder fistula were accomplished. Both ovaries were clearly identified and preserved in the procedure. The rectosigmoid and ileocolic anastomoses were performed with an end-to-end circular stapler. The patient tolerated the procedure well and was discharged home on postoperative day eight. Final pathology showed active Crohn's ileitis with fistulizing proctitis, penetrating sinus tracts, and ileorectal and ileosalpingeal fistulae (Fig).

Case 2

A 28-year-old female with a one-year history of Crohn's disease managed with asacol and steroids presented with left lower quadrant pain, fever, chills and nausea. She had localized tenderness and a leukocytosis to 16K. Her work-up included pelvic sonography, which revealed left ovarian cysts and multi-loculated fluid collections in the pelvis. A subsequent CT scan showed a thickened terminal ileum and fluid surrounding a

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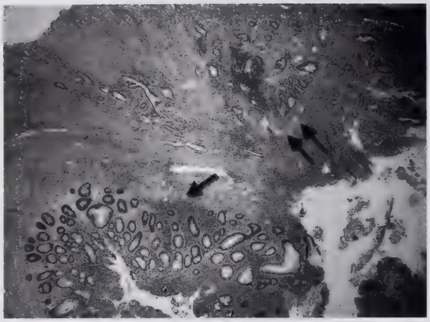

Figure. Enterosalpingeal fistula in Crohn's disease with fusion of intestinal (single arrow) and fallopian tubal (double arrow) tissues (H&E, 40×).

left adnexal mass. Sono-guided cyst aspiration yielded straw-colored fluid. Despite antibiotics the patient did not improve; exploratory surgery revealed an ileosalpingeal fistula on the left side. The ileum and left adnexa were resected *en bloc* and an end ileostomy was constructed. She had an uneventful postoperative course and was discharged home on day six. Her pathology showed severe active Crohn's ileitis and severe, active transmural salpingitis.

Discussion

In reviewing the literature, we found only one specific case report of entero-salpingeal fistula in Crohn's disease, but no case reports of U.S. origin (1). Michelassi et al. reviewed 18 years of fistulizing Crohn's disease at the University of Chicago and found two cases of enterosalpingeal fistulas out of 290 fistulas (2). Both cases were managed with *en bloc* resection. A single report from Denmark describes a tubocutaneous fistula in a Crohn's patient presenting with discharge during menstruation. These cases were also treated with fistula resection and salpingectomy (3).

The first of our two patients had a complex, aggressive presentation of fistulizing Crohn's disease with a large inflammatory mass in the pelvis and three separate fistulas from the terminal ileum to the rectum, bladder and fallopian tube, all in close proximity. The second patient presented with pelvic sepsis, and was thought to have a tubo-ovarian abscess from pelvic inflammatory disease until exploration revealed active Crohn's ileitis with an ileosalpingeal fistula. While the rectum and bladder are some of the more common sites of fistula formation in Crohn's disease, the fallopian tube is extremely rare (2). Despite a thorough history and physical exam and an extensive work-up, the enterosalpingeal fistulas were diagnosed only intraoperatively. Both cases of enterosalpingeal fistulas described by Michelassi were also diagnosed in the operating room. *En bloc* resection was the only definitive way of removing the active disease, but both ovaries were identified and preserved. These cases, as well as the previously reported cases of enterosalpingeal fistula, were treated with fistula resection and salpingectomy (3).

The lifetime risk for developing fistulas, for patients with Crohn's disease, has been reported to be 20–40% (4). Fistulas to the fallopian tubes, however, are rare and their management is not very well described. Once a diagnosis is made intraoperatively, it is very important to evaluate both ovaries. Care should be taken not to resect them unless they are involved in the disease process. Postoperatively, the patient must be told that the salpinx was resected and that her likelihood of infertility may be greater. This discussion is most important in the case of young patients of childbearing age who have not yet had children, as in our case. It is important for the surgeon operating on Crohn's disease, particularly in cases with ileal disease, to remember that fistulization between the terminal ileum and salpinx is a possibility. In the case of an enterosalpingeal fistula such as occurred in our patients, the only feasible method of clearing the disease is by fistula resection and salpingectomy.

Conclusion

Enterosalpingeal fistulas are extremely rare complications of Crohn's disease. There is only one specific case report of an enterosalpingeal fistula and two other documented cases within a large series. They are usually unexpected findings in the operating room and are rarely diagnosed preoperatively. Management includes resection of the diseased bowel as well as removal of the affected fallopian tube.

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Multimodal Characterization of a Large Right Atrial Mass after Surgical Repair of an Atrial Septal Defect

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Abstract

A 43-year-old woman with exertional dyspnea and a history of surgically repaired atrial septal defect was referred for a transthoracic echocardiogram, which demonstrated a large, mobile mass in her right atrium. The mass was further characterized with contrast transesophageal echocardiography (TEE) and delayed enhancement MRI, which together suggested a thrombus, attached to the eustachian valve and prolapsing through the tricuspid valve. The mass was resected and the diagnosis confirmed on histopathologic examination. This case illustrates the utility of a multimodal approach in characterizing cardiac masses.

Key Words: Cardiac mass, thrombus, eustachian valve, atrial septal defect, imaging, transesophageal echocardiography, cardiac MRI.

A 43-YEAR-OLD WOMAN with a history of surgical repair of a secundum atrial septal defect, two years prior, was referred for a transthoracic echocardiogram to evaluate exertional dyspnea. The echocardiogram demonstrated a large, mobile mass in her right atrium. The mass had prolapsed through the tricuspid orifice and partially obstructed right ventricular inflow. There was mild-to-moderate tricuspid regurgitation. The right ventricle was moderately dilated and hypokinetic. The mass had not been present at the time of the patient's postoperative transthoracic echocardiogram, performed 21 months earlier.

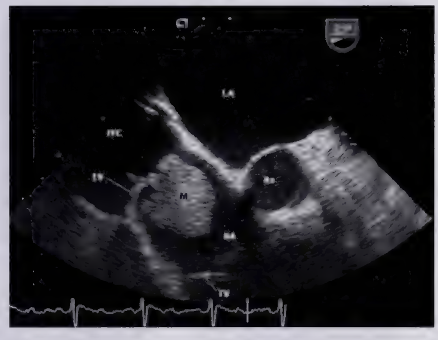

Fig. 1. Transesophageal echocardiography demonstrating an echogenic 8 cm^2 mass in the right atrium. LA = left atrium, IVC = inferior vena cava, EV = eustachian valve, M = mass, Ao = aorta, RA = right atrium, TV = tricuspid valve.

A TEE demonstrated a large, mobile mass attached to the eustachian valve (Fig. 1). The interatrial septal patch was intact and the mass was not associated with the site of repair on the septum. The differential diagnosis included thrombus, tumor and infection. The patient had no fever or constitutional symptoms, and her white blood cell count was 8.1 × 10^9 per liter with a normal differential. She had no history of hypercoagulability or prior thrombosis. However, perflutren lipid microsphere contrast injection at the time of TEE showed no significant uptake by the mass, suggesting avascularity consistent with an organized thrombus rather than a tumor.

Cardiac magnetic resonance imaging (MRI) was performed. Cine MRI confirmed the presence

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of a mass attached to the eustachian valve via a thin stalk and prolapsing into the right ventricle during diastole (Fig. 2). First-pass perfusion, performed with saturation-prepared hybrid fast gradient-echo/echo planar imaging, revealed no evidence of perfusion of the mass. Delayed enhancement MRI demonstrated an outer lamina with signal nulling at low inversion time, suggesting a relatively fresh thrombus containing methemoglobin, and an inner area with nulling at a longer inversion time, suggesting a more organized thrombus (Fig. 3).

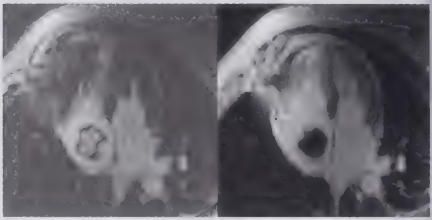

Fig. 3. Delayed-enhancement MRI images of the mass, taken 5 minutes after the administration of 0.15 mmol/kg of gadolinium diethylene triamine penta-acetic acid, using a T1-weighted, inversion recovery, gradient-echo sequence. The image on the left was obtained using an inversion time of 180 ms, while the image on the right was obtained using an inversion time of 396 ms.

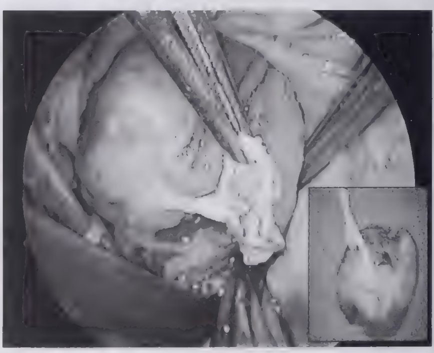

Fig. 4. Intraoperative *in situ* photograph of a pedunculated right atrial mass. There is no connection to the atrial septal defect patch, which was intact. Inset demonstrates whole specimen removed from its attachment to the eustachian valve.

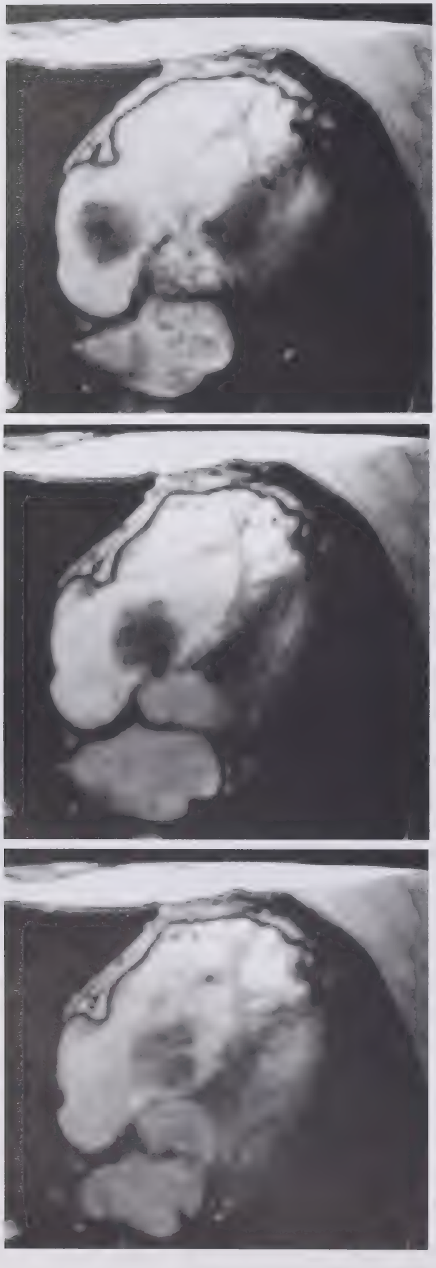

Fig. 2. MRI showing the mass in systole (top), early diastole (middle), and late diastole (bottom). Axial double-oblique views (modified four-chamber) obtained using a steady-state free precession sequence.

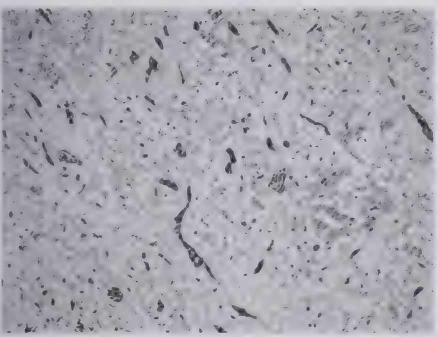

Fig. 5. Hematoxylin and eosin (H&E) stain. This fresh frozen section demonstrates an organizing thrombus with granulation tissue focally containing reactive type giant cells.

Due to the risk of catastrophic embolization, surgical excision was performed. On inspection, the mass was pedunculated and appeared to be arising from a fibrous rim of tissue presumed to be the eustachian valve (Fig. 4). After resection of the mass, a 26 mm annuloplasty ring (MC^3, Edwards Lifesciences LLC, Irvine, CA) was inserted. Histopathologic diagnosis was organized thrombus, and pathology confirmed this mass to be a thrombus (Fig. 5). The postoperative course was uneventful, and the patient was discharged on the fourth postoperative day on warfarin. No evidence of an underlying prothrombotic state was found.

Intracranial Hemorrhage Associated with Methanol Intoxication

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and Andakkan Avci, M.D.

Abstract

Methanol is a common component of gasoline, antifreeze, washer fluid, perfume, household cleaners and various other industrial products. Acute methanol poisoning produces severe metabolic acidosis, serious neurologic sequelae and rarely imaging findings. In this paper, we describe a 35-year-old man with methanol intoxication who was in a comatose stage. Computed tomography (CT) showed widespread brain edema and hemorrhages localized in the supratentorial region of the temporal lobe, nearly 3×1 cm in a crescent shape, in the white matter surrounding the capsula externa and extending to the periventricular white matter and occipital lobes. Temporal lobe hemorrhage in our patient might also have been due to the effect of heparinization during hemodialysis, metabolic and lactic acidosis, or formate.

Key Words: Computed tomography, poisoning, methanol, temporal lobe hemorrhage.

Introduction

METHANOL IS A CLEAR, COLORLESS, volatile liquid with a weak odor, slightly sweeter than ethanol. It is used in the industrial production of many synthetic organic compounds and is a constituent of a large number of commercially available solvents (1). Manifestations of methanol poisoning include visual disturbance, central nervous system depression, leading to respiratory failure, and metabolic acidosis (2). Methanol intoxication causes a variable degree of neurological dysfunction. Bilateral putaminal necrosis (rarely with hemorrhages), cerebellar and hypothalamic focal lesions and subcortical white matter demyelination have been described in cases of methanol poisoning (3).

In this paper, we describe a 35-year-old man with methanol intoxication who was in a comatose stage. Computerd tomography showed brain edema and hemorrhage in the temporal lobe and bilateral occipital lobes.

Case

A 35-year-old man with a history of chronic alcoholism was admitted to our emergency department (ED) by his relatives, who complained that his consciousness was impaired. He was admitted to our clinic 12 hours after alcohol ingestion. On admission, he was unconsciouness and cyanotic with a shallow respiration. His blood pressure was 120/90 mm Hg, heart rate 72 beats/minute, temperature 36.5°, and respiration rate 25/minute. His Glasgow Coma Scale reading was 4 (E:1, M:2, V:1). His pupils were dilated and no light reflexes were obtained bilaterally. Other physical examination details were normal.

The patient's laboratory values are shown in the Table. Nothing was abnormal on his electrocardiography, chest x-ray, lateral cervical x-ray or cerebral head tomography (Fig. 1).

The patient was intubated endotracheally. Two intravenous lines were established with 18 f gauge catheters and monitored. The patient was put on a ventilator with synchorinized intermittent mandatory ventilation mode. One hundred mg thiamine was administered intravenously. A hemodialysis catheter was placed from the femoral vein. Soon after admission, his blood pressure was 80/50 mm Hg and his central venous pressure was 0 cm H_2O; then 2,000 cc 0.09% NaCl solution was

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TABLE

The Patient's Laboratory Values on Admission

Category	Value	Normal Range
White blood cells	20.400 μL	4,300–10,300 μL
Hemoglobin	15.01 g/dL	13.6–17.2 g/dL
Hematocrit	45.8%	39.3–50.33%
Platelets	293,000/μL	156,000–373,000/μL
Glucose	377 mg/dL	70–105 mg/dL
Aspartate transaminase	26 U/L	5–40 U/L
Alanine transaminase	27 U/L	<40 U/L
Total bilirubin	0.2 mg/dL	<1 mg/dL
Direct bilirubin	0.1 mg/dL	0–0.2 mg/dL
Lactate dehydrogenase	547 U/L	160–500 U/L
Blood urea nitrogen	14 mg/dL	8–25 mg/dL
Creatinine	1.8 mg/dL	0.8–1.2 mg/dL
Sodium	136 mmol	135–145 mmol/L
Potassium	4.8 mmol/L	3.5–5.1 mmol/L
Calcium	8.26 mg/dL	8.4–9.7 mg/dL
Prothrombin time	12.1 sec	12–16 sec
APTT	34.8 sec	22.1–35.1 sec
INR	1.0	——
Arterial Blood Gases		
pH	6.63	
pO_2	85.7	
pCO_2	78.2	
HCO_3	8.2	
Methanol	66.61 mg/dL	

administered. His blood pressure increased to 100/60 mm Hg and hemodialysis was performed. Simultaneously, ethanol therapy was initiated from a nasogastric tube with a loading dose of 0.8 g/kg (280 mL of 20% ethanol). After completing the loading dose, 0.25 g/kg/h (88 mL/h) ethanol infusion was initiated. Fomepizole is not available in Turkey. Arterial blood gas analysis was done during hemodialysis, and hemodialysis was performed until the arterial blood gas analysis had been maintained at normal values for 8 hours with bicarbonate. During hemodialysis, 200 mEq sodium bicarbonate was administered to the patient; after hemodialysis his arterial blood gas results and blood methanol level were as follows: pH 7.45, pO_2 178, pCO_2 29, HCO_3 22.5 and methanol 23.54 mg/dL. Ethanol infusion was continued. On the second day of hospitalization, the patient's blood methanol level was 18.4 mg/dL, and hemodialysis was again performed, for 4 hours.

After the second hemodialysis, his arterial blood gas results and blood methanol level were: pH 7.51, pO_2 94.6, pCO_2 30.7, HCO_3 24.1, and methanol 0 mg/dL. On the third day of hospitalization, the patient's Glasgow Coma Scale reading was 3. Head CT images showed widespread brain edema and hemorrhages localized in the supratentorial region of the temporal lobe, with a size of nearly 3×1 cm and in a cresent shape, in the white matter surrounding the capsula externa and extending to the periventricular white matter and in bilaterally occipital lobes (Fig. 2). On the fifth day of hospitalization, neurology consultation was requested, since there was no spontaneous respiration and no pupil reaction. The patient was apneic and there was brain death.

Discussion

Methyl alcohol is quite toxic to humans. After ingestion, it is metabolized to alcohol dehydrogenase, then into formaldehyde and finally into formic acid (4). It is these metabolic products which have toxic effects on the body (5).

Radiological findings have occasionally been described in methyl alcohol poisoning. These include cerebral and subarachnoid hemorrhage (6), edema (7), bilateral putaminal necrosis and cerebellar cortical lesions, sparing subcortical association fibers (4, 8). Putaminal necrosis and hemorrhage result from the direct toxic effects of methanol metabolites and metabolic acidosis in the basal ganglia. Bilateral putaminal necrosis is a

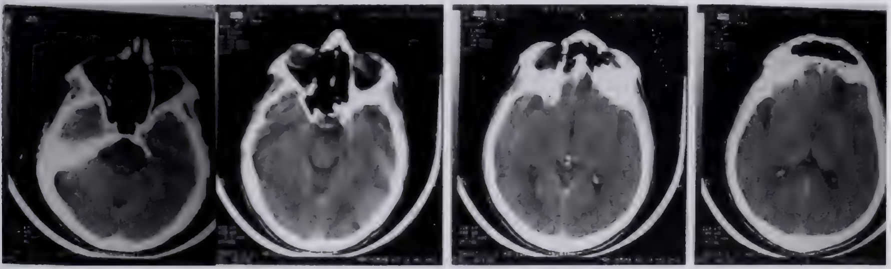

Fig. 1. Normal cerebral head tomography of the patient on admission.

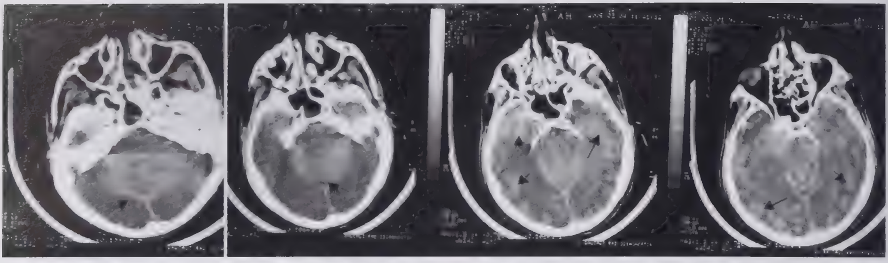

Fig. 2. Cerebral head tomography images showed hemorrhages after second hemodialysis (arrows show the hemorrhages).

characteristic feature of methanol toxicity, but can also be seen in Wilson's disease, Leigh's disease, Kearns-Sayre syndrome, and striatal degeneration associated with Leber's optic atrophy (4, 8). In our patient there was a temporal lobe hemorrhage, recorded by head CT. The appearance of hemorrhage has been reported in 13.5% of patients who have methanol poisoning (7); this might be due to the direct toxic effect of formate. The hemorrhages may start diapedically from congested capillaries and gradually enlarge. The finding of vessel congestion with vascular infiltration corroborates the effect of formate on endothelium (9). The hemorrhage in the temporal lobe and bilateral occipital lobes occured after hemodialysis in our patient. Phang et al. (7) and Giudicissi et al. (10) have attributed such hemorrhages to systemic anticoagulation during hemodialysis. However, in another study, none of the patients with methanol poisoning who underwent hemodialysis showed hemorrhagic changes in the brain. On the other hand, in the same study, CT scan of the brain showed hemorrhagic changes in the lentiform nuclei in one patient before he underwent hemodialysis (3). Although our patient's coagulation tests were normal on admission, his temporal lobe hemorrhage might also have been due to the effect of heparinization during hemodialysis. Given the results and recommendations in the literature, it may be advisable to perform hemodialysis for methanol poisoning without heparinization.

Our patient died on the ninth day of hospitalization. His catastrophic neurological state was probably due to the absorption of pure methanol, with development of intracranial hemorrhage because of delay in admission to the hospital. It seems likely that abnormalities on CT can be of prognostic value.

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Angiotensin-Converting Enzyme (ACE) Inhibitor-Associated Angioedema of the Stomach and Small Intestine:

A Case Report

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Abstract

This is a case report on a 45-year old African-American female with newly diagnosed hypertension, who was started on a combination pill of amlodipine/benazapril 10/5 mg. The very next day, she presented at the emergency room (ER) with abdominal pain, nausea and vomiting. Physical exam, complete metabolic panel, and hemogram were in the normal range. She was discharged from the ER after a few hours of treatment with fluid and analgesics. However, she returned to the ER the next day with the same complaints. This time the physical exam was significant for a distended abdomen with dullness to percussion. CT scan of the abdomen revealed markedly thickened antrum of the stomach, duodenum and jejunum, along with fluid in the abdominal and pelvic cavity. Angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema was suspected, and anti-hypertensive medications were discontinued. Her symptoms improved within the next 24 hours, and repeat CT after 72 hours revealed marked improvement in stomach and small bowel thickening and resolution of ascites. The recognition of angiotensin-converting enzyme (ACE) and angiotensin receptor blocker (ARB) intestinal angioedema constitutes a challenge to primary care physicians, internists, emergency room personal and surgeons.

Key Words: Angioedema, angiotensin-converting enzyme inhibitors, CT scan.

Introduction

WE REPORT A CASE OF angiotensin-converting enzyme inhibitor-induced visceral angioedema, which involved not only the small intestine but also the antrum of the stomach. The patient was a 45-year-old African-American female with no significant medical history. She had recently been diagnosed with hypertension (HTN) and had been started on antihypertensive drug therapy (amlodipine plus benazapril 5/10 mg) by her physician. One day after the first dose, the patient presented at the emergency room with mild, diffuse abdominal pain and vomiting. She was discharged from the ER with analgesics and advised to return if the pain persisted.

The patient returned to the ER the next day with increased intensity of pain and vomiting. A CT scan with contrast showed thickening of the antrum of the stomach and small intestine, with a large amount of ascites in the abdomen as well as in the pelvic area. To the best of our knowledge, this is the first case report of benazapril-induced angioedema involving both the stomach and small intestine. Of the previous 19 reported cases of ACEI-induced angioedema, only the small intestine or large intestine had been involved.

Case Report

A 45-year-old African American female with recently diagnosed hypertension presented at the ER with a one-day history of mild, diffuse abdominal pain and vomiting. She denied any fever, diarrhea, constipation, melena, hematochezia, rash, facial swelling or recent travel. One day prior to the symptoms, the patient had been diagnosed with HTN and started on antihypertensive drug therapy (amlodipine plus benazapril 10/5 mg). The physical examination was unremarkable. Complete blood count and comprehensive metabolic panel were within normal range. The patient was discharged from the ER with analgesics and advised to return to the ER if the pain persisted. She returned to the ER the next day with severe abdominal pain and vomiting. Physical examination revealed a distended abdomen with dullness to per-

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cussion and diffuse tenderness on deep palpation. There was no evidence of facial or pharyngeal edema. The vital signs were normal. Initial blood work drawn in the ER included a complete blood count and a comprehensive metabolic panel, all of which was within normal limits. The patient was admitted to the medical floor for further work-up of her abdominal pain and vomiting. Complement and C1 esterase inhibitor levels were within normal limits, and antiphospholipid antibody and double standard antibody tests were within the normal range. An upright film of the abdomen revealed a possible small bowel obstruction. A CT scan of the abdomen and pelvis with both oral and intravenous contrast was performed; it demonstrated marked thickening of gastric antrum, duodenum and proximal jejunum (Fig. 1) along with fluid in the abdomen and pelvis. ACEI-induced angioedema of the stomach and small intestine was suspected. The patient's antihypertensive medications were discontinued, and she was treated with IV hydration and a proton pump inhibitor. Her condition improved within 24 hours after discontinuation of the medicine. She was then started on a clear liquid diet that she tolerated well.

A repeat CT scan of the abdomen and pelvis with oral and IV contrast was done after 72 hours. It showed marked improvement in the stomach and small bowel wall thickening, with decreased ascites (Fig. 2). The patient was sent home on amlodipine. At a one-month follow-up visit, her symptoms had completely resolved.

Discussion

Angioedema of the intestine is associated with organ transplants (cardiac, renal and liver) (1, 2) and female gender (perhaps especially African-American females) (3–6). Most of the patients pre-

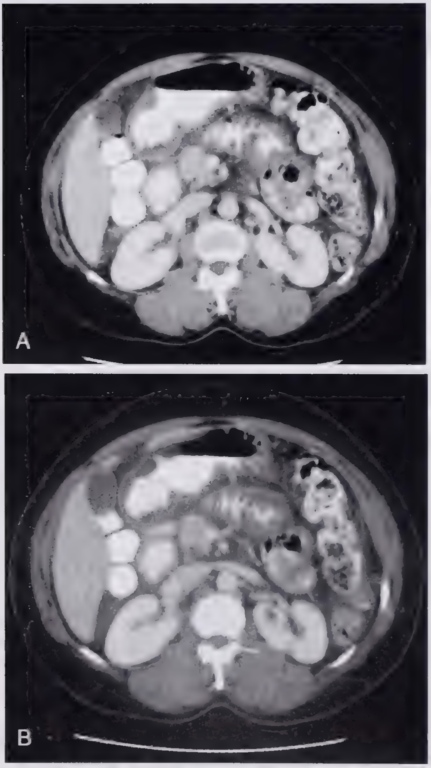

Fig. 1. Thickening of the antrum of stomach and small intestine.

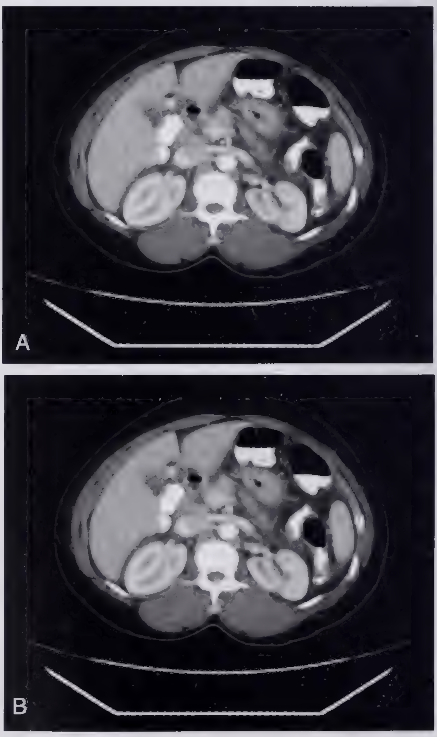

Fig. 2. Reversal of thickening of the antrum of stomach and small intestine after discontinuation of ACE inhibitor (benazapril).

sented within 48 hours of the first dose and the initial clinical symptom was generalized, diffuse abdominal pain. The incidence of ACEI-related intestinal angioedema in the general population is 0.1–0.2%, but it could be higher due to underreporting (3).

It is extremely important to suspect ACEI-related visceral angioedema in patients who develop abdominal pain while on this medication. As this case illustrates, visceral angioedema secondary to ACE inhibition is completely reversible, and its recognition may avoid unnecessary and expensive invasive investigation. According to one study, the diagnosis of visceral angioedema required surgery in 3 of 19 reported cases, and 2 of these 3 resulted in partial small bowel resections (7). There is general lack of awareness of this adverse effect. As a result the true incidence of the problem is unknown. Only 20 cases, including this case, have been reported in the medical literature in English. There have been case reports of the association of ACEI-induced angioedema with transplantation (1, 2). It appears that estrogen plays some role in causing ACEI-induced angioedema (8).

Our literature review shows that most of the symptoms start within 48 hours of the first dose and that the most common symptoms are diffuse pain (100%), vomiting (90%) and small bowel thickening on CT scan of abdomen (70%). Other common signs are ascites and leukocytosis (9, 10). None of the reported cases had stomach involvement, which is now being reported for the first time in the medical literature.

The pathophysiology of ACEI-induced angioedema is not known. Possible causes include a bradykinin-induced increase in vascular permeability (11). Early diagnosis is very important, to avoid unnecessary procedures and investigations. There is no specific test to diagnose the condition. Our patient was not rechallenged with ACEI, on ethical grounds. However, she was later prescribed a calcium channel blocker and there were no abdominal complaints after a month.

There also have been increasing reports of angioedema of the intestine caused by ARBs (12). Therefore, it is not safe to start ARB therapy for patients who have suffered from ACEI-induced angioedema.

In summary, angioedema of the gut may represent an underappreciated condition. The recognition of ACE and ARB intestinal angioedema constitutes a challenge to primary care physicians, internists, emergency room personal and surgeons.

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Guillain-Barré Syndrome Complicated by Myocarditis

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Abstract

Guillain-Barré syndrome (GBS) is an autoimmune disease affecting the peripheral nerves, and is frequently associated with triggering events several weeks prior to the onset of symptoms. We report the case of a 68-year-old female who was diagnosed with GBS and subsequently developed myocarditis. She was treated with inotropic support and intravenous immunoglobulin (IVIG), and her condition improved. This presentation of GBS complicated by myocarditis is very rare. We examined the literature regarding this association.

Key Words: Guillain-Barré Syndrome, myocarditis, cardiomyopathy.

Introduction

GBS IS AN AUTOIMMUNE DISEASE affecting the peripheral nervous system. It is associated with triggering events several weeks prior to the onset of symptoms. The most common triggers are upper respiratory and gastrointestinal infections. Known complications include respiratory failure, autonomic dysfunction, and syndrome of inappropriate antidiuretic hormone secretion (SIADH); there have been rare reports of GBS complicated by myocarditis. We report the case of a 68-year-old female who was diagnosed with GBS and subsequently developed myocarditis. This presentation of GBS complicated by myocarditis is very rare. We examined the literature regarding this association.

Case Summary

Our patient is a 68-year-old woman who initially presented to her internist with a one-week history of flu-like symptoms. This was diagnosed as bronchitis and treated with levofloxacin. Several days later, she presented to the emergency department, complaining of bilateral lower extremity weakness, lower back pain, and bilateral buttock pain. Vital signs were within normal limits. Neurological exam revealed 4/5 strength in both lower extremities and the left upper extremity, and 5/5 strength in the right upper extremity with absent deep tendon reflexes in all four extremities. The patient had a right up-going plantar reflex and decreased sensation in her right lower extremity. Laboratory tests were unremarkable except for serum sodium of 126 mmol/L. Initial electrocardiogram (Fig. 1A) was unremarkable, and initial chest X-ray (Fig. 1B) showed no acute disease. Lumbar puncture revealed no cells and mildly elevated protein (55 mg/dL), consistent with early GBS. Initial electromyogram showed an absent H reflex (the most sensitive test for early GBS), and repeat electromyogram showed diffuse demyelinating polyneuropathy, consistent with GBS.

The patient was admitted and developed progressive weakness. She later developed respiratory failure and autonomic instability, requiring intubation and monitoring in the intensive care unit. Subsequently, she manifested a new incomplete right bundle branch block and a left anterior fascicular block on electrocardiogram (Fig. 1C). Creatine phosphokinase remained normal and troponin-I increased to a maximum of 1.8 ng/mL. Transthoracic echocardiography revealed global left ventricular dysfunction. There was a moderate pericardial effusion localized around the right heart and apex. Subsequent cardiac catheterization demonstrated normal coronary arteries (Fig. 2), and a severely decreased left ventricular ejection fraction (35%) was seen on ventriculography (Fig. 3). This presentation was consistent with acute myocarditis, and so the patient was given inotropic support. After a long and complicated hospital course, and treatment with IVIG, the patient's condition improved, and she was discharged to a rehabilitation facility, with significant residual lower extremity weakness and vocal cord dysfunction.

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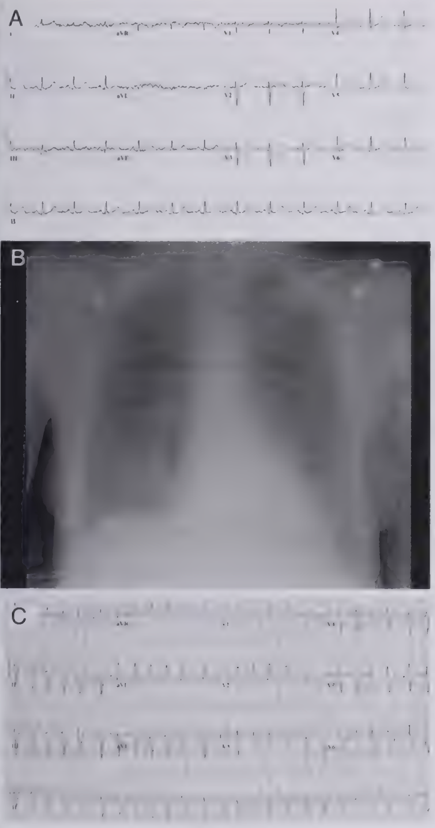

Fig. 1. **(A)** Initial electrocardiogram; **(B)** initial chest X-ray; and (c) electrocardiogram showing AV dissociation, an incomplete right bundle branch block, and left anterior fascicular block.

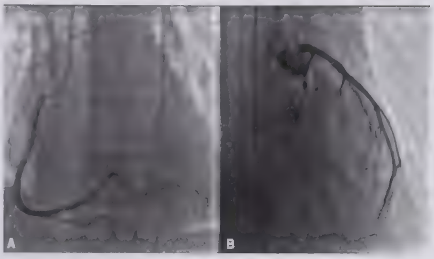

Fig. 2. **(A)** Normal right coronary artery; and **(B)** normal left coronary artery.

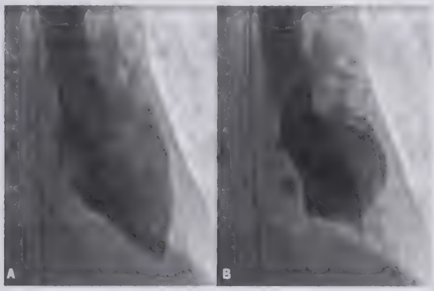

Fig. 3. Ventriculogram depicting **(A)** end-diastolic and **(B)** end-systolic frames revealing severe left ventricular dysfunction (ejection faction =35%).

Discussion

Myocarditis is most commonly the result of an infectious process, although it may also result from hypersensitivity to drugs, chemicals, radiation, or physical agents. While almost every infectious agent is capable of producing myocarditis, in the United States clinically significant acute myocarditis is most commonly caused by viruses, especially Coxsackie virus B and echovirus. The clinical expression of myocarditis ranges from the asymptomatic state associated with limited and focal inflammation to fulminant fatal congestive heart failure due to diffuse myocarditis associated with transient ST and T wave abnormalities, atrial and ventricular arrhythmias, heart failure, and death. Myocarditis may also be associated with AV conduction defects, and rarely, Q waves (1–6). Patients with myocarditis may complain of pleuritic chest pain; however, the pain may be more typical of ischemia and simulate an acute myocardial infarction with electrocardiographic changes and elevated cardiac enzymes, suggesting myocardial necrosis

To our knowledge, fewer than ten cases of GBS complicated by myocarditis have been reported in the medical literature (Table). Two cases were seen in children; one associated with infectious mononucleosis (1), and another with an upper respiratory tract infection (2). Four cases were seen in adults; one associated with gonococcal urethritis (4), another with Lyme disease (6), a third occurring with a relapse of GBS (5), and finally a case of hypersensitivity myocarditis probably secondary to the concurrent administration of phenytoin and IVIG (3).

The precise causal mechanism for myocarditis was unclear in most of the above cases. It was noted by Reimers et al. (6), in his reported cases of GBS, that myocarditis could be caused by direct invasion of the myocardium by *Borrelia burgdor-*

TABLE

Reported Cases of GBS Complicated by Myocarditis

Report	Age/Sex	Associated Conditions	Clinical Outcome	Language
Gortner[1] (1984)	10 M	Infectious mononucleosis, membranous tonsillitis, nephritis	Mild neurologic deficits	German
Hodson et al.[2] (1984)	12 M	Upper respiratory tract infection, paralytic ileus, SIADH, autonomic instability	Death	English
Koehler et al.[3] (1996)	43 M	Epilepsy, upper respiratory tract infection, hypersensitivity to phenytoin and IVIG	Death	English
Marshall et al.[4] (1975)	23 M	Gonococcal urethritis, papilledema	Full recovery	English
Okuma et al.[5] (1999)	35 M	Upper respiratory tract infection 2 years prior leading to GBS, with re-presentation two years later with an acute relapse of GBS associated with myocarditis	Full recovery	Japanese
Reimers et al.[6] (1993)	38 M	Lyme disease	Death	English
Goldman and Makaryus (Current Report, 2006)	68 F	Upper respiratory tract infection/bronchitis	Significant residual lower extremity weakness, vocal cord dysfunction	English

SIADH = syndrome of inappropriate antidiuretic hormone; IVIG = intravenous immunoglobulin; GBS = Guillain-Barré syndrome.

feri. It is also possible that the same inflammatory or autoimmune response to an infectious process was responsible for both peripheral nerve and myocardial damage. In one other case, an epileptic patient on phenytoin died after being treated with IVIG for GBS. On autopsy, he was found to have a hypersensitivity myocarditis, presumably from the interaction between phenytoin and IVIG (2).

Many patients with GBS develop autonomic instability associated with blood pressure fluctuations, postural hypotension, and cardiac dysrhythmias secondary to demyelination of the vagus and glossopharyngeal nerves, the sympathetic chain, and the white rami communicantes (2). Some GBS patients believed to have autonomic instability, based on the presence of tachycardia, may actually be developing acute myocarditis.

Conclusion

GBS is an autoimmune disease affecting peripheral nerves and is often associated with autonomic instability. Although rare, GBS has been known to be complicated by myocarditis, which is potentially fatal. If the clinician knows to include myocarditis in the differential diagnosis of the GBS patient with tachycardia and/or electrocardiographic changes, early recognition and proper treatment may prevent unnecessary morbidity and mortality.

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Painless, Acute Aortic Dissection Presenting as an Acute Stroke

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Abstract

Acute aortic dissection is an uncommon disease; however, it has a high mortality rate. Classically, aortic dissection presents with sudden and severe pain in the chest, back, or abdomen. Patients often describe tearing or ripping pain. There are a few reports of atypical findings or no pain in the literature. We report a case of painless, acute aortic dissection presenting as acute stroke.

Key Words: Painless aortic dissection, acute stroke.

Introduction

ACUTE AORTIC DISSECTION (AAD) is an uncommon, life-threatening condition, and its prompt diagnosis remains essential for successful management (1). Although acute onset of severe chest or back pain is the most common presenting symptom, it has been documented recently that some patients with AAD may present initially with painless, atypical symptoms (2–4). Establishing the diagnosis can be difficult in the presence of atypical symptoms, especially in the absence of pain. These atypical presentations include absence of pain, often in conjunction with a variety of neurological or cardiac symptoms and signs. There have been several documented cases of patients presenting with neurological or cardiac symptoms such as syncope, global amnesia, and weakness and/or paresthesia of the lower extremities (3–8). In these cases, paresis or plegia is associated with spinal cord ischemia. In this report, a case of completely painless AAD presenting as acute stroke is described.

Case Report

A 62-year-old male patient was admitted to our emergency service (ES) with left-sided weakness of the extremities and face, which occurred while he was working in his garden. He arrived at the ES three hours after the onset of symptoms. There was no history of any significant illness. On admission, the patient was drowsy (Glasgow Coma Scale score of 15/14), but cooperative and oriented. His vital signs were as follows: blood pressure 60/30 mm Hg, pulse 56 bpm and regular, respirations 22 bpm, and body temperature 36.7°C. On physical examination, there was central paralysis on the left side of the face and cyanosis at the frontal part of the neck. Cardiac auscultation revealed no murmurs, gallops or rub. The lungs were clear to auscultation. Bilateral radial and femoral pulses were palpated. Testing of motor strength in both upper and lower extremities revealed a power of 2/5 on the left, and normal on the right. Babinsky response was also positive on the left. Cerebrovascular accident was suspected, and thus no enhanced computed tomography (CT) scan of the head was obtained. However, the CT scan did not reveal any abnormal findings. The patient received supplemental oxygen (4 L/min) by nasal cannula. Crystalloids were infused via peripheral and central intravenous catheters. Following fluid replacement, his blood pressure was restored to 80/50 mm Hg. Central venous pressure was 12 cm H_2O.

Laboratory examination findings were within normal limits, except for the white blood cell count

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(14,000 /mm^3). There was no abnormal finding on his 12-lead electrocardiogram. His chest X-ray showed an apparently widened mediastinum (Fig. 1). Emergency transthoracic echocardiography (TTE) was performed at the bedside to rule out AAD. TTE showed hemorrhage anterior (21 mm) and lateral (15 mm) to the right ventricle, associated with an intimal flap extending from the aortic valve to the aortic arch. A thoracoabdominal CT scan was then performed to aid with surgical planning.

The CT images disclosed dissection extending from the aortic root to both main iliac arteries, and an expanding aneurysm at the ascending aorta (Fig. 2). While the real lumen was filled in by the contrast medium, the false lumen had not become opaque as a result of low flow in the thoracic aorta. On the other hand, at more distal levels, the false lumen was also eventually filled in by the contrast medium, and the intimal flap appeared more clearly (Fig. 3). Pericardial hemorrhage of 2 cm thickness in the cardiac levels was visualized. Also, in the upper thoracic levels, dissection extended to the origin of the brachiocephalic artery. Shortly afterwards, the patient underwent cardiovascular surgery. Cardiopulmonary bypass with hypothermic circulatory arrest was performed, using the retrograde cerebral perfusion method. A tear was located on the posterior wall of the ascending aorta just proximal to the brachiocephalic artery and the aortic dissection had extended through aortic arch and descending thoracic aorta. The ascending aorta was replaced using a Hemashield graft (Meadox Medicals, Oakland, NJ) (28 mm) with gelatin-resorcin-formalin glue. The patient had low cardiac output syndrome postoperatively and died six hours after surgery.

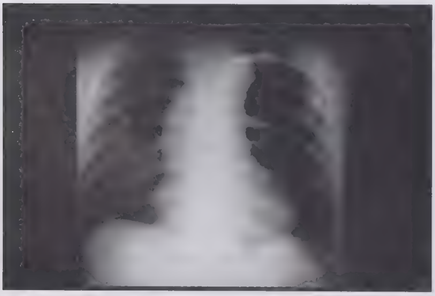

Fig. 1. The chest X-ray of the patient shows the enlargement of the aorta and increasing cardiothoracic ratio.

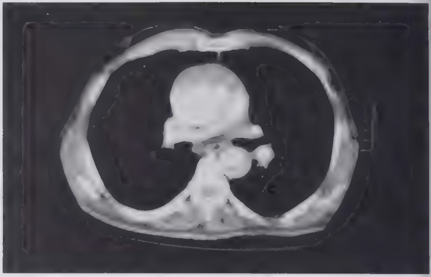

Fig. 2. The spiral CT with contrast shows an expanded ascending aorta and lumens in the ascending and descending aorta. The true lumen is seen as opacified; however, the false lumen does not opacify.

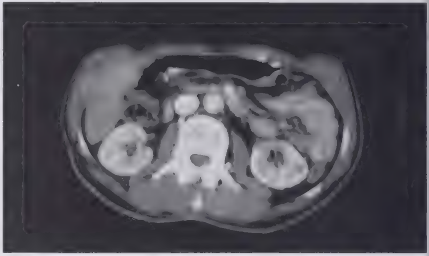

Fig. 3. On the CT at renal level, both lumens divide; an intimal flap appears to be filled with contrast material.

Discussion

The estimated incidence of aortic dissection is 5–30 cases per million people per year. Men are more frequently affected by aortic dissection, with a male:female ratio ranging from 2:1–5:1 (9). AAD often occurs in the sixth and seventh decades. It is relatively uncommon before age 40, and when it does occur it is usually in association with certain predisposing factors (10). Chronic systemic hypertension is the most common predisposing factor, which has been present in 62–78% of patients with aortic dissection. Other predisposing factors include chromosomal aberrations, hereditary abnormal connective tissue, congenital aortic valve defects, coarctation of the aorta, inflammatory or infectious abnormalities, pregnancy (especially the third trimester), annuloaortic ectasia and aortic aneurysm (9). In our case, there was no predisposing factor.

Classically, acute aortic dissection is described as presenting with a sudden onset of severe chest, back, or abdominal pain that is characterized as ripping or tearing in nature (7, 9, 11). Although, this pattern of pain is the presenting symptom in up to 90% of cases, it may occur in fewer than 10% of patients presenting with atypical symptoms (12). Our case presented no chest, back, or abdominal pain. In painless aortic dissection, the explanation for absence of pain is still a matter of controversy (13), with several explanations being offered (14, 15). Slow or gradual dissection with less wall stretching may not cause pain, and sparing of the adventitial layer, the site of aortic innervations, may result in painless dissection. Although, in the literature, there are cases of AAD presenting with neurological symptoms, all of these cases have s risk factor or pathological status for AAD (2–6, 16). Neurological symptoms include paraplegia, paraparesia, progressive motor or sensory loss in both lower extremities, numbness in the unilateral lower extremity, dysphonia, and transient global amnesia like-symptoms (2, 5–8, 17). However, in contrast to the literature, our case had left hemiparesia, with left-central facial palsy. On the other hand, there was no predisposing factor for ischemic stroke in his medical history. Neurological symptoms may be associated with the anatomic level of AAD (2–5, 9). In our case, dissection was visualized at the level of aortic valve. Thus, in this case, ischemic stroke, secondary to the dissection, might be due to a thromboembolus from this region of the aorta. No laboratory examination related to stroke was performed, because the patient died six hours after surgery.

Von Kodolitsch et al. (18) found three major criteria for diagnosis of AAD. The first is a sudden onset of pain, lacerated pain, or both; the second is a mediastinal enlargement, aortic enlargement, or both; and the third is the presence of difference in pulses, blood pressures, or both. In the chest X-ray of our case, we concluded that enlargement of the ascending aorta was a sign of AAD.

Acute aortic dissection is potentially fatal. If left untreated, AAD has a mortality rate as high as 1% per hour during the first 48 hours after onset of symptoms (19). If there is a mediastinal, pleural or pericardial hemorrhage, mortality is even more likely (20). Our patient had a pericardial hemorrhage, and he died within the first 24 hours of presentation.

Finally, in patients with painless AAD, atypical symptoms should be assessed carefully, since they may be related to AAD, as in our case, with a clinical picture of stroke. Findings in the X-rays consistent with AAD should be sought, particularly in the case of elderly patients.

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Gallstone Ileus:

A Review

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Abstract

This article aims to review gallstone ileus in the literature addressing the pathophysiology, clinical presentation, radiological findings and treatment options of the condition. A literature search was done on gallstone ileus, for the period 1966–2005. Gallstone ileus is a disease of the elderly, causing up to one fourth of non-strangulation intestinal obstructions in patients older than 65 years of age. It is often missed or diagnosed late. The presentation is that of intestinal obstruction preceded by biliary complaints. Radiological features on plain X-rays include features of intestinal obstruction and pneumobilia, and an aberrant gallstone. Treatment depends on the site of the impacted stone, but surgery is needed in many cases.

Gallstone ileus is a rare complication of a common condition. Because it primarily affects the elderly, mortality and morbidity are high, although they have improved over the years. Early diagnosis and treatment improve the outcome.

Key Words: Gallstones, fistulae, ileus.

Introduction

GALLSTONE DISEASE is a common condition, with 10% prevalence in the United States and Western Europe. It is symptomatic in only 20–30% of the cases, most commonly presenting with biliary colic. Some of the numerous other frequent complications include acute and chronic cholecystitis, mucocele and empyema of the gallbladder, acute and chronic pancreatitis, obstructive jaundice and ascending cholangitis. There are other, rarer complications that require a higher index of suspicion to diagnose, such as gallstone ileus and Mirizzi syndrome (1).

Gallstone ileus is usually a disease of the elderly, with peak incidence between 65 and 75 years of age. The youngest person reported in the literature was 13 years old and the oldest was 97 years of age. As expected, there is female predominance, since biliary tract disease is known to occur more frequently in females (2, 3). Gallstone ileus is a rare entity in the general population, but it accounts for nearly 25% of non-strangulated intestinal obstruction in patients older than 65 years of age. Being a disease of the elderly, it leads to high mortality, because of the co-morbidity of those affected. Mortality is reported to have been as high as 60% in the 19th century (1), dropping to around 40% by the 1960s and to 15–18% in the 1990s (3).

Pathophysiology

Gallstone ileus is usually preceded by an attack of acute cholecystitis, causing inflammation and adhesions in the area of the gallbladder bed. The adhesions and inflammation, with the pressure effect of the gallstone, facilitate the formation of a fistula with the small or large intestine (1). Cholecystoenteric fistulae complicate fewer than 1% of gallstones cases. The commonest fistula is between the gallbladder and the duodenum in 60% of the cases, but cholecystocolic, cholecystojejunal and cholecystogastric fistulae have also been described. In most cases the stone is passed with the stool without causing intestinal obstruction, but sometimes the stone is large enough to impact, causing obstruction (1, 3, 5). The size of the stone plays an important role in determining this; while most authors agree that stones less than 2–2.5 cm will pass without causing obstruction, stones more than 5 cm will most probably impact. The presence of strictures or abnormalities in the bowel lumen, causing it to be narrower than usual, will also increase the chances of the stone impacting (1, 6). In cases where there is clinical intestinal obstruction, the stone is most commonly impacted in the terminal ileum, which is the narrowest part of the intestine. To a lesser extent the stone may be impacted in the proximal ileum or in the jejunum, especially if the stone is big enough. Duodenal obstruction is

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relatively rare and accounts for only a minority of the cases (2, 5).

Clinical Presentation

The presentation of gallstone ileus is that of intestinal obstruction, which is usually preceded by biliary complaints. The diagnosis is usually 2–4 days late, with correct diagnosis preoperatively in only 50–75% of the cases (2, 3, 5). Clinically, the presentation may be of intermittent obstruction that improves only to reappear later. This is called the "tumbling phenomenon," in which the impacted stone is intermittently passing and lodging in the intestinal lumen and continuing to migrate distally, until the stone either passes through the gastrointestinal tract or is impacted (1, 3, 7).

Bouveret syndrome is a rare complication of gallstones, in which a cholecystoduodenal fistula forms and the stone is impacted in the duodenum, causing gastric outlet obstruction. This condition was first described in the literature by Bouveret in 1896. From then until the year 2000, only 175 cases have been described in the literature (8–10). A variant of Bouveret syndrome, in which the obstruction is secondary to the distended gallbladder, was also described (11). Clinically, Bouveret syndrome presents with signs and symptoms of gastric outlet obstruction, abdominal pain, nausea and vomiting. If the stone is not fully obstructing the lumen, the presentation will be of partial obstruction. Also the presentation may be associated with other complications of gallstone disease, such as pancreatitis. Bouveret syndrome has also been reported to be preceded by or to present as upper gastrointestinal bleeding (12–14).

Radiological Findings

Radiologically, plain abdominal X-rays are diagnostic for gallstone ileus in about 50% of the cases (5). X-ray findings of gallstone ileus were summarized by Rigler, Borman and Noble in 1941 as a tetrad of (a) partial or complete intestinal obstruction, (b) pneumobilia or contrast in the biliary tree, (c) aberrant gallstone and (d) change of the position of the previously observed stone (15). In 1978, Balthazar and Schechter described a fifth sign, which is the finding of two air fluid levels in the right upper quadrant on abdominal X-ray secondary to air in the gallbladder (16).

In Bouveret syndrome, a dilated stomach is expected to be seen on X-ray, since the obstruction is at the level of gastric outlet (17). CT scan usually shows pneumobilia, intestinal obstruction, and one or more gallstones in the intestinal lumen (13, 17). Cholecystoenteric fistulae have also been demonstrated on barium studies (8, 18), ultrasound scan (19), endoscopy (12, 14, 19–21), and endoscopic retrograde cholangiopancreatography (ERCP) (22).

Treatment

The aim of treatment of gallstone ileus is to relieve the intestinal obstruction by removing the stone. Stabilizing the patient and correcting the comorbidities are also important, to improve the outcome (1). Many approaches have been described for the stone removal in gallstone ileus: open surgery (23), laparoscopic or laparoscopic-assisted enterolithotomy (24, 25), endoscopic removal (20, 26), shockwave lithotripsy (27, 28) and lithotripsy using Nd:YAG laser (19, 29).

There are two current approaches to surgery for gallstone ileus: (a) enterolithotomy alone and (b) enterolithotomy, cholecystectomy and fistula closure in one stage. The supporters of the one-stage procedure argue that by doing the cholecystectomy and fistula closure, further attacks of cholecystitis, cholangitis and gallstone ileus are prevented. And they argue that if this is not done at the time of initial surgery, it should be done later (23, 30, 31). On the other hand, the supporters of enterolithotomy alone argue that the mortality of a one-stage procedure is higher than that of enterolithotomy alone, 16.9–19% vs. 12% (2, 3, 23). The recurrence of gallstone ileus following enterolithotomy alone is low, and so is the incidence of complications related to the persistence of the gallbladder fistula (5, 23). If there are no gallstones left, the fistula will most probably close spontaneously, provided that the cystic duct and the biliary tree are patent, allowing the bile to flow freely (2, 5). There is no consensus on the choice of operation, if needed, but enterolithotomy alone is advised especially if the patient is elderly and there are other associated co-morbidities, since it is safest to minimize the amount of surgery performed, and thereby decrease the stress of surgery and anesthesia as much as possible (5, 23).

Because of the relatively high mortality and morbidity, alternative procedures to open surgery have been suggested (19, 20, 24–29). One of these is video-assisted enterolithotomy. The procedure is started laparoscopically and the exact location of the gallstone in the intestine is identified. Then, a small incision is made on top of the stone, the small bowel exteriorized. This is followed by enterolithotomy and enterorrhaphy (24, 25).

In Bouveret syndrome the stone can be visualized on endoscopy. Some surgeons have managed to remove the stone using a basket or to break the stone into smaller stones in order for it to pass through the gastrointestinal tract (20). The stone can also be broken by using shock wave lithotripsy or laser therapy. But some argue that if the stone is broken, the smaller stones might impact distally, causing further obstruction.

Conclusion

Gallstone ileus results from an impacted stone that has reached the gastrointestinal tract through a cholecystoenteric fistula. Though it is a rare complication of gallstones, it is not an uncommon cause of non-strangulated intestinal obstruction in the elderly. Presentation is that of intestinal obstruction either preceded or accompanied by biliary complaints. The typical X-ray findings are pneumobilia, intestinal obstruction and aberrant gallstone.

Mortality and morbidity are high, although it has improved over the years. Early diagnosis improves the outcome. Treatment depends on the site of the impacted stone. If it is in the gastric outlet, then endoscopic retrieval or lithotripsy can be helpful; otherwise, open surgery, laparoscopy or laparoscopic-assisted enterolithotomy may be preferable.

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Massive Hemoperitoneum from Transhepatic Perforation of the Gallbladder

Dan Kolder, M.D., Tim Geiger, M.D., Ajit K. Tharakan, M.D., James W. Kessel, M.D., and Ziad T. Awad, M.D.

Abstract

Perforation of the gallbladder occurs in 1.6%–2.8% of cases of gallbladder disease. Transhepatic rupture of the gall bladder is rare, with fewer than 20 cases reported in literature. We report a case of transhepatic rupture of the gall bladder with massive hemoperitoneum, which required emergency laparotomy and control of hemorrhage.

Key Words: Gallbladder perforation, hemoperitoneum, transhepatic perforation.

Case Report

A 70-YEAR-OLD MAN presented to the emergency department with a five-day history of progressive abdominal pain, nausea and generalized weakness and a one-day history of repeated falls. Physical examination revealed a distended abdomen with generalized tenderness, guarding and rigidity. In addition, there was extensive skin mottling over the abdominal wall, both thighs and back. A CT scan of the abdomen demonstrated a distended intrahepatic gall bladder with enhancing walls and blood in the gall bladder fossa, Morrison's pouch and left paracolic gutter (Figs. 1 and 2).

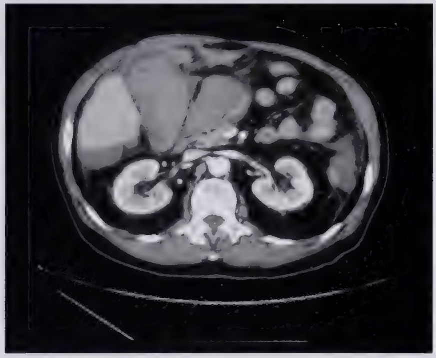

Fig. 1. Blood present in the left paracolic gutter and inferior border of liver.

An emergency laparotomy was performed, as the patient did not respond to resuscitative measures and remained hypotensive. In the peritoneal cavity there was a gush of 2 L of dark blood and several clots. In addition, there were multiple small gallstones free in the peritoneal cavity. Further examination revealed a gangrenous gallbladder that had perforated into and eroded the surrounding hepatic parenchyma, which was the source of bleeding. A cholecystectomy was performed. The necrotic liver substance was debrided, and hemostasis of the raw liver surface was accomplished using electrocautery. The patient had an uneventful postoperative recovery.

Discussion

Perforation of the gallbladder occurs in 1.6–2.8% of cases of gallbladder disease (1). The mortality and morbidity rates associated with gallbladder perforation ranges from 15–20% and 32–58%, respectively (1). Risk factors for gallbladder perforation include male gender, age above 60 years, immunosuppression, long-term steroid use, significant coronary artery disease,

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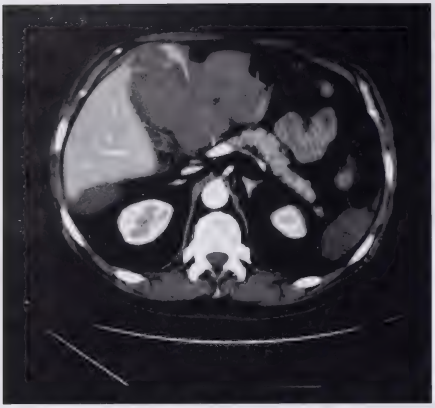

Fig. 2. Blood present in the gallbladder fossa.

malignancy, arteriosclerosis, cardiopulmonary or renal disease, obesity, diabetes mellitus and collagen disease (1).

The source of bleeding in cases of perforated gallbladder is usually the gallbladder wall or the cystic artery, due to local extension of the inflammatory process, leading to focal necrosis, rupture and bleeding (2). Very rarely, as seen in our patient and others, the source of bleeding is the liver parenchyma, through which the gallbladder had eroded.

The treatment of choice for transhepatic perforation of the gallbladder is cholecystectomy with debridement of the liver parenchyma, thus removing the source of sepsis and minimizing the potential for postoperative hemorrhage.

Transhepatic rupture of the gall bladder is rare, with fewer than 20 cases reported in the literature. However, it should be considered in the differential diagnosis of intra-abdominal bleeding, especially among patients with a history of cholelithiasis.

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Pediatric Generalism:

Emergent Issues

Danielle Laraque, M.D.

The eminent pediatrician Robert Haggerty, M.D., has recently proposed measures needed to improve the quality of care for children (1). With his ideas as background, I reflect with my colleagues in this issue of the *Mount Sinai Journal of Medicine* on some key issues confronting the discipline of pediatrics, areas of importance in pediatric care, and our vision for how we, as generalists, might change the landscape of that care.

This theme issue, entitled "*Pediatric Generalism: Emergent Issues,*" features two sets of articles, one set focusing on new training perspectives for generalists in the fields of environmental health and medical education, and the other one, on the interdisciplinary care of the "complex child," as represented by the child victim of abuse and the post-transplant child—both currently considered within the domain of the generalist. Unlike specialists, generalists must also address key health services' delivery problems, the financing of care, care coordination and community outreach. This theme issue is not meant to be comprehensive, but rather to give a glimpse into what we should hold onto as a discipline and develop within the field of generalism. All four articles have broad implications, not only for direct clinical care but for the further development of models of care and medical education.

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Forensic Child Abuse Evaluation:

A Review

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Abstract

This review discusses the forensic medical and psychological assessments of children and adolescents suspected of being victims of sexual or physical abuse/neglect. Evaluation of the whole child and the need to minimize trauma during the investigative and assessment processes are stressed. The forensic medical examination is reviewed, including the specifics of the pediatric anogenital examination. The key components of the forensic medical examination in sexual assault cases are also reviewed, with particular attention to maintaining the integrity of the process. Special emphasis is placed on the forensic interview in child sexual abuse cases, the best evidence available and areas in need of further research.

Key Words: Child abuse, child maltreatment, sexual abuse, physical abuse, neglect, forensic.

Introduction

CHILD ABUSE, CHILD NEGLECT, and their resulting physical and emotional injuries merit special attention by professionals trained in the evaluation and treatment of children and adolescents. This review presumes some knowledge by the reader of the extent of the problem of child maltreatment in the United States; detailed data are available in print and on-line from the National Center on Child Abuse and Neglect Data System (NCANDS) report of 2002 (1). The latest data from NCANDS show that there were a total of 903,089 child victims (0–18 years old) in 2001, of 3,085,693 children who were subjects of an investigation. Consensus opinion regarding this assessment has emphasized the need for a multidisciplinary/interdisciplinary approach through a team of medical, mental health, child protection and law enforcement professionals (2–6). Standardization of the evaluation process has been guided by an increasing body of knowledge regarding the circumstances of abuse, a thorough understanding of child and adolescent development, focused attention on the integrity of the forensic evidence, coordination of the investigative process, and close attention to the whole child. Minimizing physical and psychological trauma throughout the evaluation is essential. Attention to the quality of this evaluation increases the likelihood of interrupting further abuse, identifying those accountable, and, most important, improving child well-being.

The Context: Addressing the Whole Child

The field of child abuse has been advanced by considering child maltreatment as a medical diagnosis (2, 7, 8). Reaching this diagnosis requires a broad differential diagnosis; specific criteria for such diagnosis; objective assessment of the signs and symptoms; focused laboratory data; an understanding of the patterns and mechanisms of injury; in sexual abuse, the mechanics and dynamics of the abuse; and careful consideration of the consistency between the history and the medical findings (9–11). Such a process should lead to a clinical diagnosis of abuse or (just as important) a determination that the clinical findings and presentation are inconsistent with or are unlikely to be due to abuse. Thus, the approach must be to evaluate the whole child.

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Forensic evaluations in the acute and non-acute setting must be in the context of the child's needs and must endeavor not to further traumatize the child or adolescent. Child-specific techniques for completing such an evaluation have gained acceptance over the past two decades.

Additionally, the literature points to the importance of paternal support to the prosecutorial outcomes, so that support for the non-offending parent is integral to this assessment (12). The need for evaluation extending to youthful offenders (at times relatives of the victim) who may themselves be victims is also increasingly recognized (13, 14). Community resources should be called upon to further support the child, parent and family. And attention to cultural and linguistic needs is necessary in establishing the credibility of the assessment and the forensic findings.

The Forensic Medical Evaluation: Implications for Forensic Psychological Assessment

Over the past two decades, protocols have evolved for the assessment of sexual assault, sexual abuse, physical abuse and neglect of children and adolescents (4–6, 13, 15–23). These evaluations can take place in the acute or non-acute care setting. Acute care evaluations usually take place in hospital emergency departments whereas non-acute care evaluations are usually performed by multidisciplinary teams in specialty areas or child advocacy centers. The protocols guiding these evaluations call for a history of the abuse/assault/neglect; a medical history; a psychosocial history; review of systems; a comprehensive physical exam (including an anogenital exam, often aided by photocolposcopy); and collection of forensic evidence and forensic interviews (4–6, 13, 15–21, 24–26). In cases of physical abuse, description and photography of the visible external findings (e.g., ecchymoses, lacerations, fractures), radiological findings (e.g., skeletal survey, bone scan, CT/MRI findings of the head) and ophthalmologic findings (e.g., of retinal hemorrhages), are essential (2, 27, 28). Description of non-sexual genital trauma is also important. Assessment of psychological trauma (e.g., anxiety, especially post-traumatic stress, and depression) in these settings is part of a comprehensive evaluation. Appropriate disposition, including the possibility of hospitalization for the management of acute injuries and/or safety planning must also be considered. Follow-up of clinical needs and support throughout the often-lengthy family and criminal court proceedings should be available. Wherever possible, care should be coordinated with the child's/adolescent's medical home.

Step-by-step guidelines characterize the examination and the use of kits to collect forensic evidence (4, 8, 16, 27, 29–33). Since physical assault, neglect can coincide with sexual assault, and documentation of all injuries/findings is essential. Evaluation by child specialists attuned to a broad differential diagnosis and to the assessment and treatment needs of children and adolescents is required. The American Board of Pediatrics has received approval from the American Board of Medical Specialties to offer a certificate of special qualifications in child abuse pediatrics, which may have implications for those who evaluate abused youth (34).

The Anogenital Examination

Preparation for the anogenital exam of the child or adolescent requires special mention (3, 4, 6, 32, 35–37). In both the acute and non-acute setting, the child/adolescent and the parent need to have a careful explanation of this exam. Care needs to be taken to ensure confidentiality and not to compromise possible disclosure by the victim. While it is routine in many states for adolescents to seek services independently of their parents, this is not uniform across all states. The adolescent being evaluated for sexual assault/abuse must be afforded strict confidentiality in the course of both history taking and the physical examination. Without this, the evaluation for possible incest or abuse by someone known to the adolescent (familial or extrafamilial) may be compromised. The scope and limits of confidentiality, given reporting mandates, must be fully explained. The American Academy of Pediatrics Task Force on Adolescent Assault Victim Needs summarizes the epidemiology of violent injury in adolescents, its physical and emotional consequences, and appropriate care of the victim. Specific adolescent issues, psychological responses, and trauma-related disorders are reviewed (3).

Having the adolescent remain in control of his/her body and asking his/her consent for all aspects of this evaluation, including who may be present during the exam (e.g., parent, a nurse, other support person), will help maintain the integrity of the process. It is routine to ask the child who she/he would like present during this exam. This question is asked during the interview of the child alone. It is also explained to the parent that the clinician will ask the child his/her preference and will respect that choice. The child/adolescent should be offered a gown and sheet. Children/adolescents and their parents need to understand the process of the anogenital exam, including an explanation of equipment being used (e.g., photocolposcopy). It should be explained that the colposcope or otoscope/hand lens is used for external examination, and the child/adolescent should be given an opportunity to examine the equipment (e.g., turn the light on and off, visualize their hand or other object on the screen) and gain comfort with the examination. A speculum should not be used in an child who is awake, and the use of the speculum for an adolescent is based on the adolescent's wishes, comfort and experience with prior gynecologic examinations. For example, it may be appropriate to use a speculum for an adolescent who has had consensual sex for a while, but inappropriate for one who is either sexually naïve or whose vaginal orifice does not permit easy insertion. Patience in the process of examination is essential, and at no time should force or coercion be used. For young children, it may be useful to have a non-offending parent (usually the mother) assist with the exam. In some cases it is also useful for the mother or other caretaker to sit on the table and allow the child to rest her/his head and trunk on her/him. This position allows the child to see what is happening, to view the monitor when a photocolposcope is used, to see what is being done, and to be a participant in the examination. If the child/adolescent is unable to tolerate the exam, the exam should be deferred. It is advisable to set up ground rules, e.g., to tell the child that at any time during the exam she/he can ask the clinician to stop the exam or explain what is happening, or to tell the clinician that something hurts. The rare cases in which an exam cannot be deferred include children in need of urgent medical/surgical intervention (e.g., deep vaginal or anal laceration). In such cases, the examination should be conducted under sedation/anesthesia. It is important to remember that these same principles apply in the often-hectic setting of the emergency department. Adhering to this process will aid in minimizing further trauma to the child or adolescent.

Forensic Medical Examination and Kits

National, state and local guidelines address the collection of forensic information from children, adolescents and adults (30), and recommendations have also been made by the American Academy of Pediatrics (3, 5, 38). These protocols are intended to maximize the probability of collecting and preserving physical evidence for potential use in the legal system, while minimizing physical and psychological trauma to the victim. Knowledge of these protocols by the forensic medical and interviewing teams is important for several reasons. First, minimizing trauma during this part of the investigation and assuring that those procedures do not compromise later disclosures are important. Second, understanding what the child/adolescent has had to go through may be important during the forensic interviewing process and the clinical follow-up.

If sexual assault has occurred within 72 hours (and at times longer than this), the forensic medical and interview evaluations should be done in the emergency department. Abuse that is believed to have occurred prior to 72 hours or that was not accompanied by acute injuries does not require immediate assessment in the emergency department. The evaluation for non-acute presentation of abuse is best done in a specialized, child-focused center.

The evaluation done within 72 hours of occurrence of the sexual assault consists of collection by the emergency department physician/nurse of evidence using a collection kit that is sent to the crime/forensic laboratory of the medical examiner with the following: outside container with general information and labeling, victim clothing, debris, stains on skin (dried secretions), oral swabs and smears, vaginal (penile) swabs and smears, rectal swabs and smears, pubic hair brushing/combings, head hair combings, genital swab, saliva and blood specimen, reference head and pubic hair, fingernail scrapings or clippings, and nasal mucous. Other evidence may also include condoms, tampons, etc. Forms and paperwork accompany the evidence kit, documenting any findings/injuries, a brief history of the assault, prophylaxis and counseling provided. There should be documentation of any anogenital lesion and other tests sent to the hospital laboratory, which may include tests for sexually transmitted infections (STI) (e.g., gonorrhea, chlamydia, trichomonas, genital warts, herpes, syphilis, hepatitis, and HIV) (22, 36, 39–45).

Some studies of children indicate that most forensic evidence is found on clothing and linens, so aggressive search for these items in the emergency department or the home is indicated. Controversies discussed and recommendations found in specific state guidelines include trying to balance what will provide the best DNA analysis with what is reasonable and least traumatic for the victim (20, 29–32, 45–47). For example, hair samples from the head and pubic areas are obtained using one or more of the following techniques: cutting, pulling, and combing. Each technique provides a sampling of hair at a different growth stage: anagen (actively growing), catagen (resting) and telogen (ready to be shed). While telogen hair is the most likely to be transferred during an assault, anagen hair is the best for DNA analysis. In a compromise, balancing the needs of the forensic evaluation and the needs of the victim, the National Advisory Committee of the U.S. Department of Justice has recommended combing only, with the stipulation that samples should be pulled later only if a suspect is apprehended (30). Some studies have indicated that for children presenting later than 24 hours, the forensic evaluation is of little value and can be omitted (26). The effect that the forensic evidence has on criminal prosecution and what constitutes acceptable deviation from the adult protocol, for children, need further study.

As discussed below in the section on forensic interviewing, there is no consensus on whether the forensic interviewer should have knowledge of the allegations or even more detailed information. Nonetheless, knowing the specific components of the forensic evaluation is important if the investigative team is to fully understand the evidence in the case. An example of this concerns examination for spermatozoa and semen. The U.S. Department of Justice National Advisory Committee (1988) did not recommend immediate microscopic examination for sperm and motile sperm by the attending physician. Instead the recommendation was that crime laboratories with specially trained staff, sophisticated equipment and ultra-sensitive techniques that enable detection of even minute traces of semen would be better suited for obtaining these data. Following this protocol would potentially avoid inconsistent findings between the emergency department and the crime laboratory, as well as misconceptions (such as that the absence of sperm indicates no assault). The investigative team needs to be aware of the use of seminal plasma components, including the highly specific p30 prostatic antigen and the less specific acid phosphatase (31). The limitations of the use of Wood's lamp for identification of semen, the advantages of using toluidine blue to detect trauma including microtrauma, the use of culture techniques (as opposed to nonculture techniques such as DNA probe) for identification of sexually transmitted diseases (such as gonorrhea and chlamydia) the forensic use of DNA typing for infectious diseases, and the meaning of a normal or abnormal genital exam all need to be understood by the investigative team (14, 41–43). In addition, the characteristics (sensitivity, specificity, predictive positive value) of new technologies, such as nucleic acid amplification tests in the identification of STI's, must be scrutinized to determine their use in both clinical and forensic evaluations (13, 48).

The predictive accuracy of a particular test or exam finding is discussed in many articles on physical abuse (e.g., presence of retinal hemorrhages) and sexual abuse (44). The literature identifies a number of factors responsible for the presence or absence of physical exam findings at the time of the investigation of an allegation of sexual abuse or assault. First, the likelihood of finding evidence of genital trauma is increased if a child is examined within 24 hours of penetrating sexual assault, as compared to exams after 24 hours (30, 49). Semen and evidence of ejaculate are unlikely to be detected during the examination of a child, especially if the child has washed, urinated or defecated, or if the exam takes place more than 72 hours after the assault (7, 21, 22, 30, 35, 46). As noted above, the detection of sperm and motile sperm may be influenced by the expertise of the examiner. Another factor is that healing of tissue injury occurs quickly and often completely, except for the most severe injuries, so timing of the examination may affect the findings. The mechanics of sexual abuse of children often involves acts such as fondling, cunnilingus and fellatio, none of which usually leave physical findings (9–11). In fact, child molesters often utilize mechanics such as labial coitus that are unlikely to leave any signs of trauma. "Rape" refers to penetration, however slight, of the vulvar cleft and can occur without any injury to the tissue or ejaculation. The hymenal tissue's elasticity is also likely to lessen the probability that tissue injury will occur, and over time the estrogenization of the hymen will often obliterate previously abnormal findings. Non-specific findings, such as edema and erythema, can be due to abuse or non-abuse. The anal sphincter is able to accommodate the passage of stool without causing tissue trauma, so it is not surprising that anal findings are rare (50). In addition, in studies reporting cases that resulted in felony convictions for abuse, physical evidence was not present in a majority of cases, although important when present (47, 50–55). Most people in the field of sexual abuse agree that more emphasis needs to be placed on the child's description of sexual molestation and that it is this account rather than the genital or laboratory findings that will usually establish the diagnosis of abuse (22).

Forensic Interviewing: Short- and Long-Term Goals

The American Professional Society on the Abuse of Children (APSAC) has developed practice guidelines for investigative interviewing in cases of alleged child abuse (18). Likewise, states such as New York and New Hampshire have developed guidelines (20, 33). The publication of the New York State Children's Justice Task Force Forensic Interviewing Best Practices is one such example. Additionally, protocols for forensic evaluation have been proposed by many clinicians as well as through the collaborative leadership of Child Advocacy Centers (CAC), the National Children's Alliance, and individual states. As a rule these guidelines are intended as such, and not meant to be adopted as policy. There is an understanding that multiple factors, including individual case considerations and clinical expertise, must play a role in interviewing.

APSAC practice guidelines. APSAC is the best-known national, interdisciplinary society focusing on the prevention of abuse and the assessment and treatment of abused and neglected children and adolescents. Their latest guidelines, published in 2002, detail the purpose of the investigative interview, background and procedures of the interviewers, the context and content of the interview and special issues for law enforcement investigators. The reader is referred to the full guidelines, but a summary of key recommendations is presented here.

The APSAC guidelines are intended to help personnel obtain and record the disclosures of children related to abuse and determine who might have been responsible for that abuse. They provide guidance to interviewers on how to remain impartial while collecting information that may either corroborate or refute the suspicion of abuse. It is recognized that numerous disciplines have trained specialists competent to perform this interview, including law enforcement personnel, child protection services personnel, members of the district attorney's office (e.g., assistant district attorney), and child forensic interviewers (e.g., social workers, psychologists or physicians) who are members of specialized child assessment teams and have received proper training. The following broad recommendations are intended to improve the quality of the information obtained:

- The child interview should take place as close to the time of the event as possible.
- An assessment of the child should determine if he/she is physically or mentally able to be interviewed at the time of presentation.
- Careful attention to safety concerns and the impact of delay of the interview process must be considered.
- The interview should take place in a neutral place (e.g., CAC or other specialized program), if possible. This will often be dictated by the acuteness of the presentation, e.g., a child who has been assaulted within the past 72 hours should be seen in the emergency department. However, the forensic interview might be deferred for younger children in need of more preparation. The setting should provide a safe place for the child to disclose this information.
- For some children, it is possible to obtain a comprehensive disclosure in one interview. In any case, it is necessary to conduct enough interviews (and only enough) to obtain a complete and accurate story. Repeated interviews of the child by different interviewers are discouraged and may compromise the integrity of the findings.
- Accurate documentation of the investigative interview must be maintained.
- To maintain consistency of the format and record of the interview, it is generally preferable to have one interviewer.
- The interview itself consists of introductions, rapport building, developmental screening, and competency check. In the latter, some states require that the interviewer establish if the child understands or can demonstrate the difference between the truth and a lie.

The child's cognitive abilities, and developmental and trauma histories also play an important role. In these authors' experience, some children will not disclose unless sequestered and contact is denied to those who are possible offenders or have failed to protect them. The guidelines caution that the interview process should follow local protocol and legal requirements regarding parental notification about the interview, but this may be contraindicated if intra-familial abuse is suspected.

In some jurisdictions it is standard practice that the forensic interview begins with the interviewer blind to the allegations, whereas in others it is customary to have the allegations known by the interviewer. While the guidelines do not comment on which is preferable, the structure of the interview process should be at all times unbiased and support the search for alternative explanations for the findings or allegations. According to these authors, it is important to fully understand the possible mechanics (specifics of the abusive acts) and dynamics of abuse (e.g., engagement phase consisting of access and opportunity, relationship of participants, inducements, sexual interaction phase, and secrecy phase). The progression of sexual interaction from less intrusive to more intrusive is often predictable. Extreme violence and intrusive acts may characterize the clinical presentation and disclosure. The interviewer must be prepared to remain calm, not make judgments, positive or negative, about what is disclosed, and avoid negative statements or characterizations of the suspected abusers. This can be done while at the same time expressing support for and warmth towards the child. The guidelines emphasize that the interviewer should deemphasize his or her authority. Specific ground rules are often established, e.g., that the child can say he/she doesn't know or wishes to stop, or that the interviewer made a mistake.

While the guidelines state that videotaping and audiotaping may be the most comprehensive and accurate methods of documentation, they acknowledge that these methods are not universally endorsed.

In many centers, a one-way mirror or closed circuit TV allows essential investigative personnel to view the interview without having to be present in the room. If more than one interviewer is present, a lead interviewer is recommended, with a non-lead interviewer playing a minor role. Parents should not be present during the interview, but some states allow for an advocate or support person. Briefing of the parent after the interview may be possible if not contraindicated by the circumstances of the abuse. A pre-interview transition period may be needed for young children who have difficulty separating from their parents.

Preparation for the interview should include an attempt to understand a child's cultural background, relevant cultural standards including those concerning discipline and genital care, and cultural definitions, expectations and actions relevant to abuse, violence, and sexual assault. Assessment of the degree of cultural assimilation may be important. For bilingual children or those not proficient in English, a bilingual interviewer is indicated, and if not available, an experienced professional interpreter should be used, with an emphasis on precise translation.

The interviewer and team should assess any special needs that the child may have. For example, they should determine whether the child is on medication and/or needs adaptive equipment (e.g., wheelchair, helmet, hearing aid, or computer). The guidelines stress that the equipment in these cases should be viewed as an extension of the child's body. Thorough assessment of the child's cognitive abilities is required in the conduct and interpretation of the interview findings. Being attuned to the questioners' wishes and desire to please the interviewer may be seen in some children with developmental disabilities.

The guidelines review considerations regarding use of anatomical dolls and drawings, and other media, citing their use as communication tools (15). It is stressed that each case is unique and that any aid can be misused. Practitioners are encouraged to seek specialized training and information regarding varied jurisdictional legal standards. The reader is referred to suggested readings below for more details.

While there is consensus among experts regarding fundamental principles of forensic interviewing, there is little empirical evidence for preferring one protocol over another. Generally, in addition to the guidelines noted above, the interview process should allow the child to set the pace of the interview. There should be a clarification of the terms used by the child with regard to identification of individuals, body parts, or acts (e.g., "having sex"). The questioning strategy usually proceeds from "narrative invitations" (broad invitation to talk or prompts to continue, e.g., "what happened next?") or open-ended questioning, to more specific, "closed" questions. It is the experience of these authors and noted in many protocols, including the APSAC guidelines, that person- or context-focused questions are helpful in a variety of ways, including providing structure to the interview and as an aid to memory recall. It is often noted that the interviewer's decision to move from open-ended to more specific and finally direct questions must be done consciously. Whenever possible, the interviewer should attempt to return to more open-ended questioning. Safety concerns for the child usually drive the need to use more direct questioning, and the interviewer must weigh these concerns against the possible consequences in court proceedings.

The interviewer should avoid leading or suggestive questions. The guidelines define leading questions as those "that direct a child to respond in a certain way," e.g., "He touched your pee-pee, didn't he?" And suggestive questions usually provide new information that the child has not mentioned. They provide the example, "Did sticky stuff ever come out of his penis?" The authors have found that using the terms "what," "where," "when," "who" are useful, but that "why" questions should be avoided, as they may imply that the child is responsible for the actions described.

The guidelines consider the possible use of "cognitive interviewing." This consists of asking the child to picture himself/herself in the situation, to better re-create and detail what happened. If the child or adolescent has mentioned or suggests the occurrence of an event, sensory details can be elicited, e.g., what, if anything, was seen, heard, felt, smelled, or tasted. Eliciting contextual details may also prove important for possible "corroborative evidence," if recovered by law enforcement. The use of a weapon should be specifically asked about. The child may also be asked about the presence of other individuals. Again, in these authors' experience, psychological support at the time of disclosure is essential, and the child's clinical needs must always supersede the forensic needs.

Some special circumstances outlined by the guidelines are, for example, asking the child to observe a line-up. Yet the literature indicates that children have not done well with traditional police procedures. Discussions with the police and prosecuting attorney may clarify whether this technique should be used at all. The use of pretext conversations, in which a victim is asked to place a telephone call to confront the suspect, is discussed. Some states do not allow one-party consent to taping a telephone call, and the risks to the child must be carefully considered. The child may be called upon to identify specific physical evidence, for example, photographs taken with him/her present.

Several steps are listed as integral to the conclusion of the interview. First, closure of the interview on a "positive note" by shifting the discussion to more neutral topics is a strategy often found useful. Thanking the child is appropriate and giving him/her an opportunity to ask questions is also important. Finally, future safety planning and a means to contact the interviewer may be necessary.

Local guidelines and best practices. While the APSAC guidelines have proven useful, states such as New York have developed their own best practices. Funding may stipulate use of the state guidelines. The New York guidelines are not contradictory to the APSAC guidelines, but there are some notable differences.

The NY guidelines are detailed in an over-fifty-page document, with concrete examples for the interviewer. It stresses fact-finding and, like the APSAC, focuses on an unbiased, non-leading, non-suggestive interview. It advocates prior knowledge of abuse concerns, and, if possible, a discussion with the reporting source. It also stresses that a clinician involved in an ongoing therapeutic relationship with a child should be excluded as the forensic interviewer whenever possible. The interviewer is warned about not projecting adult interpretations onto children's statements. In fact, in these authors' experience, one cannot always conclude that the child experienced the abuse in a negative way, so care must be taken not to express such statements as "that must have been scary." The sections in the guidelines are similar to the APSAC's.

One subject that is emphasized more than in the APSAC guidelines is videotaping and audiotaping. The NY guidelines point out that audiotaping does not provide for documentation of nonverbal communication, and that the interviewer or a note-taker should also document, in writing, the nonverbal communication. Backup of either videotaping or audiotaping is recommended, since technical problems may arise. The need for a written policy for any agency using mechanical recording techniques is stressed. The guidelines replicate the National Children's Advocacy Center's (NCAC) pros and cons regarding recording of interviews.

In New York Criminal Court proceedings, children nine years or older are presumed capable of making a sworn statement (NYS CPL 60.20). Establishing a child's capacity to testify and his/her "swearability" (child's testimonial capacity) is required. In NY it is stressed that efforts must be made to corroborate the child's statements, to increase the likelihood of prosecution. NCAC's review points out that videotaping is an extremely useful tool at preliminary hearings in lieu of the child's appearance. These hearings occur within 72 hours of the perpetrator's arrest, and the child may not yet be mentally prepared to confront the perpetrator, as the arrest often occurs soon after the sexual assault. In 28 states, a child hearsay statute is admissible. Generally, this allows the child's statements to be repeated in court if they are found to be sufficiently reliable, and the child is available to testify and/or corroboration can be provided (e.g., a positive physical or genital exam finding). It is noted that, although the defense attorney can subpoena the child, this rarely happens. If the child is subpoenaed, the warrant may be dismissed, and the case dismissed, to avoid testimony of the child in the preliminary hearing. Videotaping may also encourage pleas from offenders who view the tape. In some states, however, children must testify in person at criminal proceedings.

The guidelines consider which written policies formal multidisciplinary teams should consider having and the Step-Wise Method of interviewing, citing Yuille and other authors such as Sattler (56, 57). The developmental assessment and other topics are presented, with practical suggestions and tables. Signs for alerting the interviewer that the child may be giving "socially desirable" answers are reviewed, such as a fixed or stereotypic response. The use of open-ended questioning is stressed. The guidelines describe the use of the "W-H chart" as a useful memory tool after an initial disclosure has been made. This is a prompt that may help the interviewer to elicit important details and assist children in organizing memories of disparate events. This simple device is basically taking a piece of with a label for the incident on top and along the side the prompts "what," "who," "where" and "when." The interviewer says something like, "Tell me everything you can remember about *who* was there during the time in the park." Questions are then asked for the other descriptors. The authors caution against the use of the word "why," as "why questions require a number of advanced cognitive skills, including self-reflection, motivations for actions, and the use of language to describe these processes."

Additional topics of interest to CAC include interpreters for forensic interviews and children's defense/coping mechanisms. Disclosure of child sexual abuse should be viewed as a process rather than a single event. The child may minimize the events at one time, deny the abuse at another time, and then give detailed accountings. None of these actions is inconsistent with abuse.

Extended forensic evaluation. As noted above, the process of disclosure can be a difficult one for many children and is often not achieved at the initial investigative interview (24, 25). Many factors, including the child's feeling of security, may impact on whether he/she is able to disclose a particular time. In some cases, a lack of disclosure has also meant the need to drop a case altogether. An extended forensic interview model developed by NCAC proposes some solutions. In this model, it is recognized that community therapists may not have had training in interviewing or forensic techniques, and may use clinical techniques that are therapeutically useful but compromise future protective or prosecutorial actions. The model attempts to standardize a process in which forensically trained therapists can assist in fact-finding. It also provides a standard framework that combines clinical and forensic techniques for complex cases. The cases appropriate for this model include factors such as the following: (a) the child does not disclose but exhibits behaviors strongly indicative of abuse, or the medical evidence is diagnostic of abuse; (b) the child does not disclose fully; and (c) the information obtained from the initial investigative work needs further clarification. Some, including the first author of this article, have written on the possible conflict between the dual responsibilities of mental health professionals (investigative vs. therapeutic), and many teams have been structured to avoid those conflicts. However, real life has dictated that a protocol be developed to address these complex cases.

The NCAC protocol includes the following phases: collection of background information, child interview sessions, rapport building, developmental assessment, social and behavioral assessment (using the Child Behavior Checklist [58], the Child Sexual Behavior Inventory [59], and the Trauma Symptom Checklist for Children [60]), focusing on the topic of concern (inventory of touching knowledge;, body parts vocabulary; abuse-focused, non-leading questions, and/or cognitive interview depending on age; filling in information gaps), testing credibility, and closure. A four-session model (one interview with non-offending caregiver and three sessions with the child) and an eight-session model (one with non-offending caregiver and seven with the child) were developed to cover the phases identified above. The eight-session model includes a session on body safety and prevention education just prior to closure. In this study on extended forensic evaluations (24, 25), the outcome categories were abuse likely, abuse unlikely, and unclear. The two former categories are considered positive results of the process.

In a pilot study, 147 cases were randomly assigned to either the four or eight sessions models, in 44.5% of the cases, a credible disclosure was obtained, with 73% of these cases supported in the legal system (24, 25). Clear information (either abuse likely or abuse unlikely) was obtained in 64% of the cases. With the eight-session model, 51% of the new disclosures were obtained by the fourth session, 77% by the fifth session, and 95% by the sixth, with no new disclosures in the seventh session, and only two new disclosures in session eight. The children in the pilot and the multi-site study ranged in age from 2–17 and 2.5–16, respectively. Applying this model more widely around the country may prove clinically invaluable. Outcome evaluations of this process will be important in determining whether this model improves both clinical and prosecutorial outcomes in real life situations.

Conclusion

This review has sought to describe current protocols for medical and psychological evaluations in case of suspected child abuse. Much progress has been made over the past two decades in the field of child abuse. The literature continues to indicate that only a minority of cases go to trial. In case flow analyses, most cases were accepted for prosecution, and a large proportion carried forward for prosecution resulted in guilty pleas (12, 57, 61). In one study using bivariate analyses, cases likely to be dropped have involved young children, boys, certain ethnic groups (e.g., Native American), and a family member as the alleged perpetrator. Research is needed using multivariate analyses of these kinds of data. Continued diligence in improving the investigative and prosecutorial processes is critical. Research findings must be translated to the clinical situation to improve the forensic investigative process in this most difficult area.

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Pediatric Organ Transplant Patients and Long-Term Care:

A Review

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Abstract

We review the role of the academic generalist in the care of the child or adolescent who has undergone an organ transplant. This care is seen within the context of the "medical home" and the special considerations for pediatric patients. These special considerations include growth and development, psychosocial adjustment, cardiac and renal complications, endocrine problems, medication management and regimen adherence, infectious complications, vaccination, post-transplant malignancies, post-transplant lymphoproliferative disorders, acute post-transplant complications, recurrence, contraception and pregnancy for adolescents, and transition to adulthood. Research needs in this complex area are highlighted.

Key Words: Organ transplantation, pediatrics.

Introduction

IN 2004, 1,816 PEDIATRIC TRANSPLANTS were performed in the United States alone. These patients represented 7% of all transplants performed that year. This number has been steadily increasing over time—a 30% increase over the prior ten years. In addition, the survival rates of pediatric transplant patients continue to improve, with rates comparable to those of the adult transplant population, with the exception of small bowel transplants. Being in a pediatric age group should no longer be considered a risk factor for poor outcomes following transplantation (1). With this is mind, it is important for pediatricians to be aware of the issues that will confront these unique patients. These patients will seek a stable "medical home,"[1] in addition to their transplant centers. Generalists will certainly have the opportunity to care for a patient with a solid organ transplant. One of the most important ways to facilitate this care is for these pediatric generalists to feel comfortable communicating with the transplant specialists about how to best offer patients comprehensive and quality care.

Background

In a recent overview of the state of pediatric transplantation as of 2004 (1), the most commonly performed organ transplants were renal (cadaveric and living related) and liver (cadaveric and living related), with heart, lung, heart and lung, and small intestine (with or without liver) following. Kidney transplantation survival rates have climbed to 93% for one-year survival and to 76% (living) and 65% (cadaveric) for seven-year survival. For liver transplant patients, the 5-year survival ranges from 79–87%, which exceeds the survival rate for adult recipients. Children now compose 12% of all heart transplants and have an unadjusted one-year sur-

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[1] Medical care of infants, children, adolescents and young adults that is acceptable, continuous, comprehensive, family centered, coordinated, compassionate and culturally effective; care that is delivered or directed by well-trained physicians who provide primary care and help to manage and facilitate all aspects of pediatric care; and led by a physician known to the child and family, working in partnership through mutual responsibility and trust (American Academy of Pediatrics). (Pediatrics 2002; 110 (1):184–186.)

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vival rate of 70–89%, depending on age at time of transplantation.

Special Pediatric Considerations

In caring for the medical needs of pediatric transplant patients it is important to be aware of unique problems they may experience and how common problems may be affected by their immunocompromised state. They may also have different presentations or more significant outcomes as compared to adult patients.

Growth

Most children have problems with growth prior to receiving the organ transplant, due to their underlying chronic disease/ill health. The use of growth hormone is commonly indicated for patients with significant delay in growth. Many children have significant metabolic bone disease (especially renal and liver patients), and others may have congenital or metabolic syndromes that are associated with short stature/poor growth, which are not completely corrected by the transplant. After the transplant, a rule of 25% is understood: 25% will have persistent growth failure, 25% will become obese, and the remaining 50% will usually show dramatic catch-up growth and normalize their weight percentiles. Poor growth can be seen by the 6-month-to-one-year period after transplant, with catch-up growth occurring within 1–4 years. On average, final height remains lower than that of non-transplanted adults (2). Often the best predictors for linear growth are an age < 2 years at the time of transplant, pre-transplant nutritional status and stature, steroid use and graft function (2).

Patients who have been recipients of solid organ transplants have generally had problems with growth and especially with metabolic bone disease—from either chronic liver or chronic kidney disease. It is important to ensure that pediatric transplant patients receive adequate calcium supplementation and vitamin D and avoid immobilization. Post-transplant adult patients continue to have problems with osteopenia and osteoporosis, due to the medications needed to maintain immunosuppression. Much work is being done on using bisphosphonates to improve bone integrity. Interestingly, in pediatric transplant patients, the results have been contradictory. A study done by D'Atiga et al. on children after liver transplant revealed that they showed an initial reduction in bone mineral density (BMD) scores, similar to adults after transplant. But they then showed an increase in BMD 12 months or more after transplantation and reached normal levels in all but one patient. All patients had increased markers of bone turnover and reduced levels of vitamin D (3). In addition, those patients with increased BMD had an increase in linear growth. However, those patients who were already post-pubertal grew less and had less improvement in BMD.

Helenius et al. have done a survey illustrating that post-transplant children were found to have an increased risk of spinal scoliosis compared to the population as a whole. The relative risk of scoliosis needing treatment (a curve >20 degrees) was 17.0 (CI 6.75–42.7) for a transplant patient compared to an age-matched control (4). Thus transplanted patients should continue to be screened for scoliosis, despite a recent U.S. Preventive Services Task Force recommendation against routine screening for scoliosis (5). In addition, transplanted patients tend to have more complicated scoliosis repairs and less complete correction (6). The dental needs of children after transplant must also be assessed, with early referral to a pediatric dentist, consistent with the American Academy of Pediatrics recommendations.

Development

When looking at the functional level of post-transplant children, 50% of patients are found to be functioning at least one grade level lower than peers. Twenty-five per cent (25%) of these children are diagnosed with learning problems, and 35% of patients with biliary atresia will have some form of developmental delay. Clinical predictors of worse outcome in the first year after transplant are malnutrition and, not surprisingly, a prolonged in-hospital course (7). While caring for the post-transplant patient, it is important to keep these concerns in mind. The timing of the transplant can impact the development of the patient. Infants may have problems with caregiver attachment that can cause stress on the parent-infant bond, due to frequent hospitalization. Normal development can be assessed by the Bayley scales of infant development, tracking mental and motor development (8). Motor delay tends to persist throughout the first year after transplant and is most pronounced in children less than 6 months old with liver transplant. This may be due in part to the mechanical effect of the transplant-abdominal incision, hepatomegaly and ascites (2). Close monitoring of neurologic development, with referral to early intervention, and complete evaluations for hearing and vision impairment are essential.

Normally, during the toddler years, important motor, language, cognitive and social milestones are met. For children after-transplant, physical mobility may be diminished, a problem often exacerbated by fewer chances for communication/interaction with same-aged peers. When they are toddlers, disruptive behaviors can appear and must be dealt with to improve patient and parent functioning. Early school age children engage in cognitive and social processes that are essential for normal development (8). Extended school absences with subsequent re-entry can lead to school refusal, separation anxiety and concern regarding appearance. Children at this age are forming social relationships with their peers, and transplantation can sometimes decrease these opportunities. A balance needs to be found between health concerns and adequate activity in school and other extra-curricular opportunities. In a study by Wray et al., 25–40% of heart and heart/lung transplant recipients experienced behavioral and academic problems, which persisted as long as 5 years after transplant (9). In general, post-transplant patients tend to have a normal IQ score within 5 years after transplant. But they also tend to have greater problems with language ability and memory (2). Approximately 30% of liver transplant patients are a grade behind their peers, and 20% of recipients require special education (2).

Adolescents frequently have problems regarding identity, body image, sexuality and emerging independence. As noted by Green and Ray (10), 75% of transplanted children complained about the cosmetic affects of the immunosuppressant medications. These can include hirsutism or alopecia, gingival hyperplasia, weight gain, stretch marks, scars and hernias. These cosmetic effects may affect adherence to medication, particularly during adolescence, the period that presents the highest risk of decreased compliance with immunosuppressant medication and the highest risk of graft loss. Adolescents need to be screened for depression and anxiety, and presented with interventions to help them manage anger and stress, and improve coping skills (8).

Psychiatric studies of psychosocial adjustment found that fewer children had adjustment problems if their transplant occurred before the age of 8 years. These children were more likely to consider themselves similar to their peers. After this age, there was an increased incidence of adjustment problems (11). In addition, a recent article by Shemesh et al. demonstrated that depression is frequently underrecognized by caregivers and physicians caring for transplanted patients. At least 10% of patients have experienced some depression, anxiety and post-traumatic stress disorder (12).

Cardiac Hypertension and Cardiomyopathy

It is well known that the drugs used to induce immunosuppression have been associated with hypertension in post-transplant patients. Hypertension occurs in approximately 30% of children following liver transplant, approximately 10% of whom will require hypertensive medication (2). Patients should be monitored at least annually at a minimum and after every adjustment to their immunosuppressant regimen. The choice of hypertensive regimen should be dictated based on the patients other co-morbid conditions (asthma, diabetes, hyperlipidemia, gout) and side effect profile (e.g., hyperkalemia). It is important to note that if calcium channel blockers in the non-hydropyridine class are used they can interfere with the level of immunosuppressance. It is best to avoid verapamil or diltiazem if possible. If they must be used, drug levels of cyclosporine/tacrolimus must be followed after each dosage change. Inadequately controlled hypertension is certainly a risk factor for future cardiovascular disease and should be carefully monitored and controlled.

Endocrine/Diabetes

The drugs used to induce immunosuppression in the transplant patient put the patient at increased risk of developing diabetes. Some pediatric patients will develop diabetes while on both high-dose steroids and high-dose tacrolimus in the immediate post-transplant period. It is important to realize that their risk of diabetes does not completely disappear once they are weaned off high-dose steroids. Calcineurin inhibitors and especially tacrolimus, interfere with insulin secretion. In a review done by Avitzur et al. (13), 10% of pediatric patients were found to have diabetes at ten or more years after transplant. For this reason, the post-transplant patient should have yearly screening for diabetes with fasting glucose and/or hemoglobin A1C. The practitioner should have an increased index of suspicion if a patient develops polyuria and/or polydipsia. In addition, the patient should be counseled to maintain a healthy weight based on body mass index measurements and to maintain an active lifestyle.

Hyperlipidemia

Both steroids and calcineurin inhibitors increase patients' risk of elevated cholesterol and increase their long-term risk for atherosclerotic disease. The risk is especially high for the cardiac transplant patient (90%), moderate for the renal patient (70%), and lowest for the liver patient (10%). Most heart transplant patients are automatically started on statin therapy after transplant. Preliminary studies appear to indicate that statins can be used safely long term. Annual screening of lipid panel should be done in all transplant patients.

Renal

The most important long-term concern for transplant patients is the effect of the calcineurin inhibitors on renal function. These drugs cause renal insufficiency due to arteriolar nephrosclerosis and interstitial fibrosis. Patients can have an immediate decrease in glomerular filtration rate (GFR) after transplant due to vasoconstriction, and the GFR progressively decreases over time. In addition, renal insufficiency in the immediate post-transplant period is fairly common (14). A recent study also reported that hepatitis C associated glomerulonephritis is probably underdiagnosed in the immediate transplant period (15). The incidence of chronic renal insufficiency (i.e., creatinine > 2.5) is approximately 8% in the adult transplant population. The incidence of end-stage renal failure is reported to be as high as 9.5 in some transplant series (16). In the review by Avitzur et al. looking at pediatric liver transplant patients 10 years after transplant, 50% had a decreased GFR with moderate renal insufficiency and 4% had severe renal failure (13). It is recommended that a bun/creatinine evaluation and urinalysis be conducted annually. Care should be taken to avoid nephrotoxic agents, and dose adjustments of all medications should be based on the patient's changing renal function.

Medication

It is important for the pediatrician to have a basic understanding of the commonly used immunosuppresants and their major side effects. Most transplant regimens will contain a calcineurin inhibitor (CSA, tacrolimus) or an mTor inhibitor (rapamycin or sirolimus) plus either a steroid or a "steroid sparing" agent (azathioprine or mycophenolate). The possibility of drug interactions must always be avoided. Either choose an alternative drug or, if unavoidable, recheck the CSA or tacrolimus level to assess for need to adjust up or down. Coordination with the patient's transplant center is of course essential. In choosing antimicrobial agents, it is important to recall that some induce calcineurin inhibitors (isoniazid, rifampin, nafcillin), thus lowering therapeutic levels and increasing risk of rejection. Others inhibit the patient's metabolism and thus increase the risk of toxic levels (macrolides, anti-fungals), and finally some antibiotics cause renal toxicity, which can be dose related, idiopathic or synergistic. Again, most important, checking and following calcineurin inhibitor levels will be the key to successful management.

Compliance

Compliance is a major concern for any physician caring for patients with chronic medical conditions and should be assessed periodically. Special attention should be paid to fluctuating levels of immunosuppressant, ideally before there is any impact on graft function. Potential risk factors that impact family compliance are history of substance abuse, school dropout, child abuse, single parent, and economic stresses. Adolescence is a particularly difficult period for many patients with chronic disease and may be partly responsible for lower graft survival rates in this age group (17).

Infection

As noted by Marty and Rubin (18), one of the factors that have allowed transplantation to progress has been the advances in controlling infectious disease in the transplant patient. "Prevention of infection whenever possible with prophylactic or preemptive antimicrobial therapy and prompt diagnosis and aggressive treatment of invasion when prevention fails are key pillars." In their review, they demonstrate a timetable for approach to infections in the post-transplant patient. The key periods are the first month after transplant, 1–6 months, and then six months or more. Interestingly, in the first month after transplant, the patient is at high risk not for opportunistic infections, but rather those infections stemming from complications of the surgical procedures (wound infection, catheter infection, etc.) or unrecognized infection in the patient before transplant. The second time period is characterized by lingering infections secondary to anatomic or technical abnormalities, onset of viral infections (especially cytomegalovirus [CMV], Epstein-Barr virus [EBV], human herpesvirus 6, Hep B, Hep C and HIV) and then the beginning of opportunistic infections by Pneumocystis and Aspergillus. These infections occur as a result of sustained immunosuppression and the effects of the co-infecting viruses (18). Prevention requires prophylaxis with trimethoprim and sulfamethoxazole (TMP/SMZ) and control of CMV and EBV replication and invasion. In the final time period, 6 months or more after transplant, infections fall into 3 types: patients with normal functioning grafts (80%) are at risk for community-acquired respiratory infections; 10% have a recurrence of hepatitis B or C; and those few with poorly functioning grafts (10%) are at highest risk for opportunistic infection (18).

When treating infections in the post-transplant patient, it is often necessary to use empiric therapy—a best guess approach. These regimens depend on the clinical syndrome (pneumonia, urinary tract infection, bacteremia), the timing after transplant and local factors of the site in which the patient is being treated (i.e., resistance patterns) (18). One should first assess if the patient has a therapeutic emergency, with emphasis on resuscitation of the patient, immediate assessment and culturing, and broad-spectrum bactericidal therapy (18). Once the patient is stable and improving, reassessment and narrowing of regimens can be done 3–5 days later.

Vaccinations (Routine)

It is actually most valuable if pediatric patients can receive most of their primary vaccination series before transplant, due to decreased efficacy in the immunosuppressed patient. That being said, many patients have not been able to receive these vaccinations due to ill health and uncertainty in the timing of the transplant. Ideally, live vaccines are not given within 2–4 weeks of the transplant, and it is not always clear when a pediatric patient will actually receive an organ. Campbell and Herold recently published recommendations for the solid organ transplant candidate, including starting many of the vaccines before the usual age and at an accelerated rate (19).

Most centers begin to resume the vaccination of the post-transplant patient 6 months after transplant. Usually the patient has been tapered off high-dose steroids and has reached a more stable level of immunosuppression by this time. A complete review has been done by Burroughs and Moscona (20). It is not usually necessary to restart any vaccine series that have already begun before transplant. In general, killed and component vaccines are safe to give to the transplant patient. These vaccines include formulations of the diphtheria, tetanus and acellular pertussis vaccine, *Haemophilus influenzae* type B, hepatitis B vaccine, hepatitis A vaccine, inactivated polio vaccine (IPV), pneumococcal vaccine (both 23 valent Pneumovax and 7 valent conjugated Prevnar) and both forms of the meningococcal vaccine (quadrivalent Menomune and conjugated Menactra).

Although vaccines have been shown to be less immunogenic in patients with lowered immune systems—whether it be immunosuppression from steroids or from AIDS—it is not customary to assess for immunity after vaccination for most vaccines, with the exception of hepatitis B and hepatitis A vaccines. Evidence and recommendations for checking and re-boosting patients for the hepatitis B vaccine come mostly from the hemodialysis literature. Patients found to have waning protective antibody levels to hepatitis B SAb have benefited from booster vaccination.

It is important, however, to remember not to give live vaccines to the post-transplant patient. These include vaccines for measles, mumps and rubella (whether singly or as the MMR vaccine), varicella, the oral polio vaccine (which is no longer routinely given in the U.S.), the live attenuated influenza vaccine (via the nasal route), and the new rotavirus vaccine being developed. Although there has been some investigation into using live vaccines, the studies have been small and limited. There has been a single report of giving the varicella vaccine to patients following solid organ transplants (21). In addition, there have been small studies evaluating measles vaccine in both renal transplant and liver transplant patients (22). However, the current recommendation do not recommend offering these vaccines until larger studies have shown a favorable risk-to-benefit ratio.

Patients' family members should receive all live virus vaccines if they are not already immune, with the exception of the live oral polio vaccine, which can be shed. It is reasonable to check transplant patients' titers to see what they might still be susceptible to and thus avoid exposure. This is done universally before transplant at centers in the U.S.; this information can often be obtained from the transplant specialist. If this information is not available, it is reasonable to check these titers to know what the patient is vulnerable to and offer immediate post-exposure prophylaxis as indicated. Letters of medical waiver should be given to schools or camps, as appropriate.

Respiratory syncytial virus (RSV) vaccine is not available yet, but RSV prophylaxis should be considered, as appropriate. There have been no reported studies yet looking specifically at solid organ transplant patients. It has been recommended to target high-risk candidates for treatment: children < 1 year old, those with significant lung disease and children being transplanted during the RSV season.

There is a recent study on recommendations for "travel vaccinations" for the post-solid-organ transplant patient (23). It is not uncommon to need to decide if your patient should be offered malaria prophylaxis and other protection prior to traveling outside the U.S. Recommendations can be checked at the cdc.gov website for travelers, based on the country of travel. It is usually strongly recommended that patients receive hepatitis A vaccine, if they haven't already received it. They may also receive the yellow fever, Japanese encephalitis, rabies, and parenteral typhoid and cholera vaccines, if indicated. They should not, however, receive oral typhoid vaccine or oral cholera vaccines, which are live vaccines. And under no circumstances should a patient receive the bacille Calmette-Guérin vaccine (BCG) vaccine. Letters of medical waiver should be given to the patient. In addition it is helpful to give your patients a summary letter of their medical condition and a list of medications. It is, unfortunately, not uncommon for travelers to lose their medication abroad, and a summary letter can sometimes facilitate their emergent replacement. Live vaccines, as noted above, are contraindicated, but killed vaccines, such as those for meningococcal, rabies, and Japanese encephalitis virus, are occasionally recommended for travel and may be given.

Cancer

The immunocompromised patient is at increased risk of developing cancer. Post-transplantation lymphoproliferative disorder (PTLD) is the most common form of cancer in children, while skin cancer is the most common in adults. Transplant patients are at increased risk for non-melanoma skin cancer, especially squamous cell and basal cell cancer. A population-based study done on all transplanted patients in Ireland between 1994 and 2001 revealed a significant increase in the incidence of cancer compared to age-matched controls. It showed that the incidence of non-melanoma skin cancer (NMSC) had two peaks: the first peak after two years following transplant for patients older than 50 years, but more important, a second peak after 6 years for patients younger than 50 years. But this second group had a relative risk 200 times that of age-matched controls (24). The usual higher prevalence of basal cell vs. squamous cell carcinoma (SCC) is reversed in transplant patients. In this study, the risk of invasive SCC was 82 times higher than that of the non-transplant population. This and other studies have highlighted the importance of educating patients regarding the significant increased risk of developing cancer and urging them to avoid unnecessary sun exposure. In addition, they need to receive systematic examinations for early detection of skin lesions.

PTLD is probably the most feared complication of solid organ transplant in the pediatric population, but strategies have been developed for surveillance of EBV titers and adjustment of immunosuppression with detection of elevated titers. Most pediatric transplant centers now have standardized protocols. As a result of these advances, the incidence of PTLD has decreased from 15% to 5–10% of children. Survival has also been improving thanks to treatment involving both decreased immunosuppression, antiviral therapy and monoclonal antibody rituximab (22). Risk factors for the development of PTLD are the following: age <5 yr at time of transplant, primary EBV infection after transplant, and an EBV positive donor graft. Prolonged use of high-dose immunosuppression and anti-lymphocyte antibody are also risk factors (2). What is important for the academic generalist to recognize is that PTLD can present in subtle ways. Presentation can be with onset of unexplained fever, weight loss, failure to thrive or diarrhea, new onset seizures, pneumonia or airway obstruction with progressive lymph node enlargement. It is important to discuss these symptoms with the transplant centers to consider evaluation for PTLD, in addition to usual childhood illnesses. The adenoids, tonsils and gastrointestinal tract are the most common locations for presentation of PTLD, according to a study by Avitzur (13). Academic generalists who manage patients both in the inpatient and outpatient settings need to be alert to subtle and more typical presentations of PTLD.

Other cancers that are more prevalent in solid-organ-transplant patients include cervical cancer, lung cancer (especially bronchogenic carcinoma in lung and heart transplant patients), renal cancer, and lymphoma.

Transplant Complications

Most complications will occur within the first 6 months of the transplant, whether they are surgical problems, acute rejection or significant infection. However, rejection and infection are problems that can occur even years after the transplant.

Recurrence of Primary Disease

The recurrence of the primary disease is more often a problem for adult patients who have been transplanted secondary to chronic viral hepatitis B and C. However, patients with autoimmune hepatitis and patients with systemic lupus erythematosus can have a recurrence of disease in the transplanted organ.

Puberty and Contraception

Following liver transplantation, it can take up to five years for young girls to attain normal puberty, and most girls will experience menarche one to two years later than average. Those who have already reached menarche will have normal menstrual cycles return soon after transplantation (2). It is important to note that fertility may resume as early as 3 weeks after transplant, so discussions of appropriate contraceptive methods should occur prior to transplantation. Hormonal contraception can be offered to the patient, with progesterone only being the drug of first choice. Depo progesterone can be used but its effect on decreasing bone density and increasing weight gain must be considered. Combined estrogen/progesterone (E/P) tablets are another option for a teenage patient. Although combined E/P tablets can induce or exacerbate jaundice or biliary tree problems (2), they are less dependent on precise timing of administration and more "forgiving" in a teenaged population. If combined agents are used, the lowest dose of estrogen in a monophasic pill is preferred, to avoid fluctuating levels of calcineurin inhibitors. The medication should ideally be used continuously, to avoid drug-free intervals, which would affect calcineurin levels. Use of condoms is always recommended, to avoid exposure to sexually transmitted infections. Intra-uterine devices are more likely to fail in patients taking immunosuppressive agents and are not recommended. Other barrier methods are available but have been shown to be used less effectively by adolescents. Emergency contraception can be used by the transplant population.

Pregnancy

Ideally, conception should be postponed for one year, until the majority of post-surgery complications/rejections have been passed. As noted in the review by McKay and Josephson, at this time the risk of rejection is low, the dose of immunosuppressive medication is at its nadir, viral prophylaxis has been completed and the patient is generally stable (26). The consensus of the Women's Health Committee of the American Society for Transplantation was that pregnancy is safe after the first year, provided that allograft function is stable and that no rejection episodes have occurred in the year before conception. By this point, pregnancies are usually successful, but often complicated by hypertension, pre-term delivery and low-birth-weight infants (26). All solid organ transplants should be followed by a "high-risk" obstetrician, in close coordination with the transplant specialist.

Prognosis

Adolescence is one of the biggest challenges in any chronic disease population. It has been discouraging that the adolescent population still has the lowest survival rates for any of the transplant populations. The actual reason for this is unclear, but it is speculated that a major problem is compliance with the complicated medication regimen and the need for frequent follow-up and testing. It is also possible that some of the changes occurring during puberty may affect the metabolism of the medications. It is important to try to provide the patients in this age group with additional support and time. There is also an urgent need to focus on educating both the parents and the teen and later the young adult dealing with a chronic disease.

Compliance

Five complex factors play a significant role in increased noncompliance. They are: prevalence of side effects of the medication, reduced social support, pre-transplant noncompliance, low socioeconomic status, and certain psychological/personality traits (anxiety, depression, cognitive disorder or avoidant coping strategies). A 2002–2003 study in one center found that male sex, high stress from adverse effects, fair self-rated health, and fair social support were the most predictive of noncompliance (27).

In children, the most common individual characteristics of nonadherence are adolescent age, low self-esteem, depression/anxiety, poor communication/socialization skills and lack of acceptance of diagnosis. Familial characteristics include single parent, family instability, lack of social/emotional support, low socioeconomic group, and poor intra-family communication (28). Kalb and Loeber have defined pediatric nonadherence as those instances when a child either actively or passively, but purposely, does not perform a behavior that has been requested by a parent or other adult authority. Willful nonadherence is the intention to defy established limits. To achieve a successful transition from childhood to adolescence and then adulthood, adolescents must develop a number of important skills. These include cognitive development, abstract thinking, and the ability to see and assume the short- and long-term consequences of their own behaviors. Adolescents must develop the capacity to visualize the future consequences of their current actions, something difficult in a healthy teen, let alone one who is chronically ill and perhaps emotionally delayed (29).

Transition

Health-related quality of life (HRQL) generic childhood screening has been done in various transplant populations. There are no tools specific to transplant patients. HRQL after liver transplantation is lower than in the general population and in comparison to other children with chronic diseases (2). Research is beginning to focus on how best to help this population of patients; one strategy involves looking at models used for patients with problems such as congenital heart disease, cystic fibrosis or sickle cell disease. The important task is to assist these patients in finding a medical home as they go through this transition period. They will need to deal with finding new medical providers at the same time that they are grappling with emotional issues, advanced education, employment and financial issues. It will be important for the pediatrician or adolescent specialist to help them find a new medical home. Research will be needed to help formulate chronic care models in support of the complex needs of transplant patients to achieve desired health outcomes.

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Training Needs of Pediatricians Facing the Environmental Health and Bioterrorism Consequences of September 11th

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Abstract

Objective: The September 11, 2001, terrorist attacks have been called "the worst environmental disaster in the history of New York City." As a result of the extensive nature of the destruction, our objective as pediatricians was to determine the experience and training needs of tri-state child health professionals in responding to the environmental health and bioterrorism-related demands placed on their practices.

Methodology: American Academy of Pediatrics members in New York, Connecticut, and New Jersey were sent either a web-based or a paper survey requesting demographic data and data about post-9/11 practice experience and perceived knowledge with regard to environmental health and bioterrorism.

Results: Of the 1,396 respondents, 21% believed their practices to have been "very [much] affected" by the attacks. Eleven percent were often/very often asked by parents about air quality, 12.6% about environmental toxins, 4.3% about antibiotics for anthrax, and 4.2% about potassium iodide for nuclear events. Fifty-seven percent and 49.1% of respondents had patients present with environmental health and bioterrorism-related complaints, respectively. Most (86%) reported that their medical training had not sufficiently prepared them to meet these demands. Few considered themselves to be knowledgeable about bioterrorism (23.9%), local environmental issues (14%), air quality (11.4%), or environmental toxins (12.6%). Gender, race, practice setting, practice location, specialty, and level of training were associated with demands on practice. Location, age, years in practice, and gender were associated with level of preparedness.

Conclusions: Our results indicate that nearly all child health professionals would benefit from post-disaster education, especially trainees. A role for the pediatric associations in the dissemination of this crucial information is implied.

Key Words: Children, environmental health, bioterrorism, toxins, disaster preparedness, September 11.

Introduction

THE EVENTS OF SEPTEMBER 11, 2001 represent the most serious terrorist attack on American soil, resulting in massive destruction in lower Manhattan. The World Trade Center (WTC) and several surrounding buildings were reduced to more than 1,500,000 tons of debris (1, 2). Fires from the buildings, started by the initial combustion of 90,000 L of jet fuel, continued to burn for 99 days, their toxic plumes sustained and amplified by burning office materials and diesel exhaust from continuously operating rescue and recovery machinery and vehicles (3). Highly alkaline dust consisting of pulverized cement, glass fibers, asbestos, lead, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, organochlorine pesticides, and polychlorinated furans and dioxins blanketed the city (4), settling inside homes, schools, and workplaces. Thus, the events of 9/11 have been described by the New York Committee for Occupational Safety and Health as "the worst environmental disaster in the history of New York City" (5).

Following the attack, fears of biological manifestations of terrorism and concerns about the environmental consequences of the attacks emerged. In October 2001, community residents filled public forums with questions about the area's health hazards (3). Seven local schools delayed their reopenings due to parents' objections about the air quality (6). Moreover, at this time anthrax appeared in United States Post Offices and other locations, sparking discussions of bioterrorism preparation. Among Google's top queries that month were "anthrax" (#1), "milzbrand" (#4), "cipro" (#5), and "smallpox" (#7) (7). Today, public anxieties remain: a *New York Magazine* cover story, describing increased incidences of respiratory, renal, cardiac and oncologic ailments among

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first responders, asks, "What if [they] aren't the only ones to get sick, but the first in a mutely expanding ring?" (8).

The Environmental Protection Agency has admitted that its September 18, 2001, declaration that the air was "safe" lacked "sufficient data and analysis" to support it, had been "revised to eliminate cautionary statements," and "only applied to...healthy adults—not sensitive sub-populations such as children" (9). In a recent survey, many New Yorkers reported a lack of confidence in information provided by the government (45.1%) or police/fire departments (31%) regarding evacuation decisions (10). In situations such as these, people often look to their physicians to advise them on matters of health and safety. With regard to children, who for behavioral, dietary and physiologic reasons are more susceptible to toxic exposures than adults (11–13), the need for medical guidance is especially clear.

Primary child health professionals (CHP) are the most likely population to field questions from parents about environmental and bioterrorism risks and exposures for children. However, very little in the literature addresses the ability of these practitioners to answer such questions. To further elucidate the training needs of pediatricians following "the worst environmental disaster in the history of New York City," we conducted a pilot survey of New York, New Jersey, and Connecticut members of the American Academy of Pediatrics (AAP) about their perceived knowledge, skills and training deficits in caring for children and families directly affected and/or anxious about post-September 11 environmental and bioterrorism health consequences. We hypothesized that pediatricians would experience environmental health and bioterrorism-related demands on their practices, but would acknowledge an inadequacy of training and knowledge in responding to these concerns.

Methods

Data Collection

The data for this study come from a survey of members of the AAP. The methodology has been discussed elsewhere (14). Of the 8,556 AAP members in good standing from the New York, Connecticut, and New Jersey chapters, all those with listed e-mail addresses (n=4,330) were e-mailed a hyperlink to the web-based survey, while a random sample (n=1,320) of those without them (n=4,226), were sent an identical survey via postal mail. A total of 1,553 survey responses were received, yielding cooperation rates of 26% and 43% for the e-mail and postal samples, respectively, and a weighted, combined rate of 36%. Those who were not seeing patients were eliminated (n=157), leaving a final database of 1,396. Data collection occurred between September and December 2002. All protocols were reviewed and approved by Institutional Review Boards at the Mount Sinai School of Medicine and the New York Academy of Medicine.

The 42-item survey inquired about demographic information, personal and practice experience with 9/11, prior training characteristics, training needs (knowledge and skills), and perceived barriers to delivery of health services. In this paper, we concentrate on questions dealing specifically with 9/11-related environmental health and bioterrorism experiences: respondents' self-assessments of disaster preparedness and the number of children, if any, that they identified with environmental health problems related to the attacks. All survey questions were pre-tested among 125 attendees of a New York City educational conference meeting related to the needs of CHP following the 9/11 attacks, several months before the survey was undertaken.

Independent Variables

We included three demographic variables in our analyses: gender, age, and race/ethnicity. We dummy-coded gender, with male as the reference group. Age was divided into five categories: less than 35, 35–44, 45–54, 55–64, and 65–74 years. Race/ethnicity groups, originally coded as White, Asian, African-American, Hispanic/Latino, Native American and Other, were combined into White, Asian and a general "Other" category (representing African-American, Hispanic/Latino, Native American, and Other Race/Ethnic groups, due to their small frequency in our sample), with White as the reference group.

We also assessed the following practitioner characteristics: practice location, specialty, years in practice, and practice setting. Location was determined by two variables from the AAP membership database: (a) The respondent's AAP chapter, defined as *NY District 1*: counties north of Dutchess; *NY District 2*: Queens, Brooklyn, Nassau County, and Suffolk County; *NY District 3*: Staten Island, Manhattan, Bronx and counties south of and including Dutchess; *New Jersey*; or *Connecticut*; and (b) Zones characterized by proximity to the WTC site, assigned by the first practice zip code listed by the respondent. Using these questions, we coded respondents into six location areas: Manhattan, the four outer NYC boroughs, downstate NY (ten lower counties exclusive of NYC), upstate NY, Connecticut and New Jersey. Practitioner specialty was coded as pediatric generalist, pediatric subspecialist, or pediatric resident. Years in practice was divided into the following categories: 5 years or less, 6–10 years, 11–20 years, 21–30 years, and over 30 years. Primary practice setting was coded as community hospital, university hospital, private practice, or "other" setting.

Dependent Variables

The analyses focused on three measures of "demands placed on respondents' practices" and two variables assessing "knowledge about environmental health issues" related to terrorist attacks. The first two demands questions inquired about the percentage of each respondent's patients presenting complaints about environmental health and bioterrorism issues. For all of our analyses, we dichotomized responses, based on an examination of the variables' frequency distributions, into two categories: those who stated that 5% or less of their patients had the complaint and those who stated that more than 6% of their patients had the complaint. The survey also asked the extent to which patients requested medical information about air quality, environmental toxins, antibiotics for anthrax, and potassium iodide for nuclear events (coded 1, very little, to 4, very often). These items were factor analyzed, found to assess one underlying dimension, and averaged into a Patient Demands on Environmental Health Issues scale, with a range from 1–4 (Cronbach's alpha = 0.74). We dichotomized the scale into two groups: respondents who averaged 2 or less on the four-item scale (very little/somewhat) vs. those who averaged more than 2 (often/very often).

Of the two knowledge measures, the first asked if participants felt sufficiently informed to provide "general information" about the health effects of the World Trade Center Disaster (WTCD) to their patients, with "no/uncertain" coded 0 and "yes" coded 1. Respondents were also asked about their level of knowledge (coded 1, not knowledgeable, to 4, very knowledgeable) regarding four WTCD environmental issues: bioterrorism, environmental issues, air quality, and environmental toxins. Factor analysis yielded one concept, and averaged to form a Knowledgeable about Environmental Health Issues scale (Cronbach's alpha = 0.83). This scale was also dichotomized into respondents who averaged 2 or less (low/somewhat knowledgeable) vs. those who averaged more than 2 (knowledgeable/very knowledgeable).

Statistical Analysis

Statistical Package for Social Sciences (SPSS, Inc., Chicago, IL) was used to conduct all analyses. The data were weighted based upon the sampling fractions of e-mail and mail responses. Chi-square tests were performed to establish bivariate associations between the 7 independent and 5 dependent variables. Multiple logistic regressions with odds ratios (ORs) and 95% confidence intervals (CIs) were used to determine the effect of independent variables on demands on practice and knowledge, controlling for other variables in the model. Although not shown, all analyses control for data collection modality (mail vs. internet). Interactions with various demographic variables (age, gender, race and practice location) were also examined; however, since none of the interactions achieved statistical significance, the additive model is reported below. We discuss our nonresponse analysis in a previous paper (14).

Results

Practitioner Characteristics

Female respondents were slightly more numerous (54.7%) than male (45.3%). Of all age groups, the lowest three were the most strongly represented: 23.1% were under 35, 29.2% were 35–44, and 29.3% were 45–54, while 15.1% were 55–64, and 3.2% were 65–74. White practitioners accounted for the vast majority (70.5%) of the study population, with Asians (17.1%) the second largest racial group, and the "Other" category comprising 12.4%. Half of the survey participants worked in either the NYC/Long Island area (26.9%) or in downstate New York (24.9%). Other areas demonstrated a smaller, but substantial, response: 19.8% from upstate New York, 16.2% from New Jersey, and 12.2% from Connecticut. Most respondents were general practitioners (71.1%), but responses were also collected from pediatric subspecialists (21.2%) and residents (7.7%). The survey population showed a range of years of experience in practice: 31.1% had 5 years or less, 14.3% had 6–10 years, 29% had 11–20 years, 19.9% had 21–30 years, and 5.7% had over 30 years. Half were in private practice, over one quarter (26.6%) worked in university hospitals, and about one tenth worked in community hospitals (13.2%) or other settings (10.2%).

Analyses showed that a significant proportion of the respondents had fairly high demands placed on their practices after the WTCD with regard to environmental issues, but less than a quarter felt knowledgeable/very knowledgeable about these issues (top half of Table 1). Specifically, more than 17% of the respondents indicated that 6% or more of their patients came to them with environmental complaints and nearly 13% reported that an equally high percentage of patients presented with bioterrorism complaints. In addition, nearly 11% reported fielding questions "often" or "very often" from parents about air quality, 13% about environmental toxins, 14.3% about antibiotics for anthrax, and 4.2% about potassium iodide for a nuclear event. Lastly, 11% reported patients seeking information with similar frequency about at least two of these four environmental/bioterrorism issues.

Respondents' ratings of knowledge and preparedness for community disasters are shown in the bottom half of Table 1. Nearly half (49.1%) believed themselves to be too uninformed to provide general information to their patients about the health effects of the WTCD. A fairly small minority rated themselves "knowledgeable" or "very knowledgeable" about bioterrorism (23.9%), environmental issues in the immediate area of the WTCD site (14%), air quality (11.4%) and environmental toxins (12.6%). Overall, only about 27% of the respondents considered themselves "knowledgeable" or "very knowledgeable" on two or more of these issues.

Bivariate Associations

Bivariate associations between the seven predictor variables and the five outcomes are shown in Table 2. As can be seen, all of the predictors were significantly related to at least two of the outcomes variables. Males, whites, upstate New Yorkers and pediatric subspecialists were less likely to report significant percentages of their patients presenting with environmental and bioterrorism complaints than females, minority physicians, NYC practitioners, and generalists or residents. In addition, CHPs working in community or university hospitals were less likely to have 6% or more of their patients presenting environmental or bioterrorism complaints as compared to pediatricians working in private practice or other settings. Finally, Asian physicians, NYC and downstate NY CHPs, generalists, and private practitioners were more likely to have patients seeking information about two or more environmental health issues "often" or "very often" than other minority physicians, pediatricians in other locations, pediatric subspecialists and residents, and practitioners in hospitals or other settings.

TABLE 1

Impact of 9/11 on Respondents' Practice and Their Perceived Knowledge about Environmental Issues Surrounding the World Trade Center Disaster

Demands about Environmental Issues	Valid Percent (n)*
Patients Presenting Environmental Complaints	
0–5%	82.5 (1149)
6% or more	17.5 (244)
Patients Presenting Bioterrorism Complaints	
0–5%	87.3 (1215)
6% or more	12.7 (177)
Parents Seeking Information about Air Quality	
Very Little/Some	89.2 (1209)
Often/Very Often	10.8 (147)
Parents Seeking Information about Environmental Toxins	
Very Little/Some	87.4 (1187)
Often/Very Often	12.6 (171)
Parents Seeking Antibiotics for Anthrax	
Very Little/Some	85.7 (1163)
Often/Very Often	14.3 (194)
Parents Seeking Potassium Iodide for Nuclear Event	
Very Little/Some	95.8 (1294)
Often/Very Often	4.2 (57)
Parents Seeking Information/ Medication for Two or More Environmental Issues	
No	89.0 (1208)
Yes	11.0 (150)
Knowledge	
Feels Informed to Provide General Info about Health Effects of 9/11	
No	49.1 (667)
Yes	50.9 (693)
Knowledgeable about Bioterrorism	
Not/Somewhat	76.1 (1049)
Knowledgeable/Very Knowledgeable	23.9 (329)
Knowledgeable about Environment	86.0 (1182)
Knowledgeable/Very Knowledgeable	14.0 (193)
Knowledgeable about Air Quality	
Not/Somewhat	88.6 (1212)
Knowledgeable/Very Knowledgeable	11.4 (156)
Knowledgeable about Environmental Toxins	
Not/Somewhat	87.4 (1197)
Knowledgeable/Very Knowledgeable	12.6 (172)
Knowledgeable about Two or More Environmental Issues	
No 73.4 (1012)	
Yes 26.6 (366)	

*All percentages and frequencies reflect weighted data.

In terms of knowledge, males, whites, respondents 45–64, and CHPs who have been in practice

TABLE 2

Bivariate Associations between Predictor Variables and Practice Demands and Knowledge Outcomes

Variables	**Patients Presenting Environmental Complaints** **% 6%+**	**Patients Presenting Bioterrorism Complaints** **% 6%+**	**Parents Seek Info about 2+ Environmental Health Issues** **% Often/ Very Often**	**Sufficiently Informed to Provide Info about WTCD Health Effects** **% Yes**	**Knowledgeable about 2+ Environmental Health Issues** **% Knowledgeable**
Gender					
Male	13.9***	8.7***	10.1	60.4***	34.2***
Female	20.6	16.1	11.8	43.0	20.4
Age					
Less than 35	21.4	16.5	11.0	45.4**	20.0**
35–44	15.1	13.6	10.1	48.4	25.1
45–54	18.3	9.6	11.4	56.4	30.6
55–64	14.7	11.4	11.9	56.3	30.4
65+	15.5	13.3	11.1	38.6	33.3
Race/Ethnicity					
White	15.0***	11.0**	9.6***	54.3***	26.6
Asian	23.4	17.9	18.9	38.8	27.9
Other	23.5	15.3	9.1	49.1	24.7
Practice Zone					
Manhattan	23.5***	12.7***	19.4***	58.6	39.9***
NYC 4 boroughs	27.2	14.6	13.8	44.4	29.5
NY Downstate	16.7	18.2	14.8	54.5	22.7
NY Upstate	8.7	4.3	2.7	52.7	18.5
Connecticut	18.1	5.6	9.1	52.1	29.7
New Jersey	13.8	16.5	9.2	48.3	26.6
Specialty					
General Pediatrics	18.6***	15.6***	13.1**	52.9	25.6***
Pediatric Subspec.	9.9	4.3	6.9	49.5	34.4
Resident in Training	26.2	13.5	7.7	41.0	16.8
Years in Practice					
5 years or less	21.7	15.9	11.0	43.8**	22.4***
6–10 years	14.1	12.6	9.8	47.9	16.8
11–20 years	17	11.0	11.7	53.7	32.7
21–30 years	14.9	11.3	9.6	58.3	28.4
over 30 years	12.8	8.9	11.7	57.1	38.5
Practice Setting					
Community Hospital	15.8**	6.0***	7.5***	46.2	31.1
University Hospital	15.9	8.7	6.8	49.4	28.6
Private Practice	16.6	16.7	14.9	52.9	24.0
Other Setting	28.9	12.6	7.4	50.7	28.6

* $p<0.05$
** $p<0.01$
*** $p<0.001$, χ^2 test

longer tended to see themselves as sufficiently informed to provide general information about the effects of the WTCD on their patients' health (Table 2, column 4). Interestingly, there was no statistically significant association between this outcome and practice zone or setting. Males, respondents 45–65, practitioners from Manhattan, pediatric specialists, and those in practice longer indicated that they had more knowledge about environmental health issues (Table 2, column 5). Race and practice setting were not statistically related to this outcome.

Multivariate Logistic Regression Results

Logistic regression models for the three practice demand outcomes and two knowledge outcomes were estimated (Table 3). After adjusting for practitioner demographics, practice characteristics and survey modality, caring for patients with environmental complaints was predicted by gender, race, practice zone and specialty (Table 3, column 1). More specifically, women and Asians were more likely to have 6% or more of their patients

TABLE 3

Multivariate Logistic Regression Odds Ratios and 95% Confidence Interval (CI) for Independent Variables Related to Demands and Knowledge

Dependent Variables	**>6% of Patients Presenting Environmental Complaints**			**>6% of Patients Presenting Bioterrorism Complaints**			**Parents Seeking Info about Environmental Health Issues**			**Informed to Provide General Info about WTCD Health Effects**			**Knowledge of Environmental Health Issues**		
Independent Variables	**OR**	**CI**	**P-Value**	**OR**	**CI**	**P-Value**	**OR**	**CI**	**P-Value**	**OR**	**CI**	**P-Value**	**OR**	**CI**	**P-Value**
Gender															
Male	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Female	1.56	1.21-2.18	0.009**	2.22	1.50-3.28	0.000***	1.38	0.92-2.05	0.116	0.54	0.42-0.69	0.000***	0.52	0.39-0.68	0.000***
Age															
Less than 34	1.09	0.27-4.34	0.907	0.81	0.12-2.50	0.779	2.20	0.44-11.03	0.337	4.69	1.70-12.90	0.003**	1.38	0.46-4.13	0.570
35–44	1.12	0.30-4.13	0.867	0.91	0.16-2.65	0.999	2.13	0.47-9.66	0.327	4.46	1.73-11.45	0.002**	1.71	0.63-4.65	0.293
45–54	1.53	0.45-5.17	0.495	0.58	0.11-1.52	0.392	2.06	0.50-8.47	0.317	4.07	1.69-9.83	0.002**	1.69	0.67-4.28	0.265
55–64	1.03	0.33-3.17	0.063	0.64	0.14-1.54	0.429	1.50	0.42-5.34	0.535	3.01	1.36-6.66	0.007**	1.48	0.65-3.39	0.354
65+1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—	
Race/Ethnicity															
White	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Asian	1.54	1.03-2.28	0.034*	1.44	0.93-2.24	0.103	2.06	1.31-3.24	0.002**	0.67	0.48-0.93	0.017*	1.39	0.98-1.99	0.069
Other	1.49	0.95-2.32	0.079	1.33	0.80-2.19	0.271	0.80	0.42-1.50	0.483	0.96	0.67-1.39	0.839	0.94	0.61-1.44	0.772
Practice Zone															
Manhattan	1.85	1.02-3.24	0.030*	0.82	0.43-1.54	0.533	4.07	2.16-7.66	0.000***	1.43	0.92-2.21	0.112	1.77	1.13-2.79	0.013*
NYC 4 boroughs	2.36	1.46-3.80	0.000***	1.05	0.63-1.75	0.862	2.20	1.22-3.97	0.008**	0.90	0.62-1.32	0.593	1.19	0.79-1.79	0.417
NY Downstate	1.36	0.83-2.21	0.222	1.06	0.66-1.69	0.810	1.89	1.09-3.28	0.023*	1.18	0.82-1.68	0.379	0.80	0.53-1.20	0.280
NY Upstate	0.62	0.34-1.15	0.130	0.25	0.12-0.51	0.000***	0.32	0.13-0.81	0.016*	1.08	0.73-1.57	0.711	0.52	0.32-0.82	0.005**
Connecticut	1.55	0.87-2.76	0.134	0.26	0.11-0.58	0.001**	0.99	0.47-2.07	0.979	1.02	0.66-1.58	0.921	1.10	0.69-1.76	0.694
New Jersey	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Specialty															
General Pediatrics	0.78	0.44-1.45	0.436	1.28	0.59-2.76	0.528	1.24	0.50-3.13	0.643	1.40	0.82-2.40	0.216	1.60	0.84-3.04	0.152
Pediatric Subspecialty	0.40	0.20-0.80	0.010*	0.41	0.16-1.01	0.053	0.87	0.32-2.33	0.778	0.85	0.49-1.47	0.562	1.67	0.87-3.22	0.124
Resident in Training	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Years in Practice															
5 years or less	1.15	0.38-4.08	0.810	1.22	0.32-4.63	0.773	0.56	0.15-2.06	0.382	0.31	0.13-0.72	0.007**	0.43	0.17-1.06	0.068
6–10 years	0.80	0.27-2.87	0.712	0.95	0.25-3.58	0.937	0.49	0.14-1.78	0.280	0.42	0.18-0.96	0.041*	0.31	0.13-0.76	0.010*
11–20 years	0.98	0.38-3.23	0.974	1.21	0.36-4.05	0.756	0.61	0.20-1.92	0.400	0.47	0.22-0.99	0.048*	0.61	0.28-1.31	0.203
21–30 years	0.94	0.45-3.02	0.899	1.42	0.50-4.04	0.506	0.54	0.20-1.45	0.223	0.70	0.36-1.34	0.279	0.52	0.27-1.00	0.049
over 30 years	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Practice Setting															
Community Hospital	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
University Hospital	1.16	0.66-2.06	0.604	2.18	0.98-4.86	0.057	0.84	0.37-1.88	0.665	1.25	0.82-1.92	0.302	1.01	0.64-1.59	0.964
Private Practice	1.56	0.91-2.70	0.109	3.99	1.89-8.41	0.000***	2.83	1.37-5.81	0.005**	1.06	0.71-1.60	0.773	0.75	0.48-1.15	0.187
Other Setting	1.81	0.96-3.42	0.068	2.27	0.96-5.37	0.063	0.90	0.35-2.31	0.821	1.04	0.62-1.74	0.879	0.92	0.53-1.61	0.772
N	1,281			1,280			1,251			1,252			1,266		

N = 1,396, providers actively seeing patients
* p ≤0.05
** p<0.01
*** p<.0001, χ^2 test

presenting environmental complaints than males and whites. Respondents practicing in NYC were also more likely to have patients with environmental complaints, while pediatric subspecialists were less likely to see such patients. Women and private practitioners were more likely to have patients with bioterrorism complaints, whereas respondents in upstate New York and Connecticut reported hearing the same concerns less often (Table 3, column 2). Asian and private practitioners were more likely to have patients seeking information about environmental health issues than whites and those practicing in community hospitals. Not surprisingly, CHPs practicing in NYC and downstate New York were significantly more likely to have patients seeking environmental health information, while those in upstate New York and Connecticut saw fewer patients seeking such information (Table 3, column 3). Finally, it should be noted that respondent age and years in practice were not significantly related to any of the three practice demand outcomes.

The multivariate results for the two knowledge outcomes reinforced the bivariate analyses findings. Those who reported seeing a relatively high percentage of patients seeking environmental health information also tended to be the respondents who felt the least informed about such issues. Practitioners who perceived themselves as sufficiently informed to provide general information about the health effects of the WTCD were younger than 65 years. Females, Asians, and those in practice for fewer years perceived themselves to be less informed. Females, upstate New Yorkers, and those who had been in practice for the least amount of time perceived themselves to be less knowledgeable. Of note, neither specialty nor practice setting was significantly related to the two knowledge outcomes.

Discussion

Our study, the first to address health professionals' readiness to address post-September 11 environmental and bioterrorism-related issues, indicates a substantial impact of the event on pediatric practices—more markedly on those in geographic proximity. Our data show that patients, particularly those in NYC, presented with environmental complaints, while parents in NYC and downstate NY sought information about environmental health issues. Bioterrorism complaints were also seen in the NYC, downstate NY and NJ regions. These results are supported by various media representations of public concern in these areas (3, 6–9). Surveys of New York state residents concur that such urgency for information exists: Boscarino et al. report that 61% of those surveyed would seek vaccination for smallpox if it were available, and 30% would flee if the threat of biological or nuclear attack arose (10). As in our study, this fear of biological and nuclear terrorism was accentuated in the NYC and Long Island areas (15).

As hypothesized, AAP members, predominantly pediatricians, reported a lack of knowledge in the face of questions about air quality and environmental toxins—concerns that are linked, but certainly not exclusively to, the September 11th attacks. Environmental issues are attendant upon many aspects of modern and industrialized life; lead, automobile exhaust, cigarette smoke, occupational exposures, demolition/construction debris, and radiation from home appliances are commonly encountered on a daily basis. A brief review of the literature verifies such a critical, yet unfulfilled, educational need. Chai et al. (11) surveyed pediatricians, family practitioners, naturopathic physicians, school nurses, public health officials, Parent-Teacher Association presidents, and Head Start parents in the Northwest Pacific region, and found that despite the importance of the issue (64% felt that environmental exposures contribute to children's illnesses) and the ranking of medical specialists as the first information resource used, almost half (48%) of parents stated that their providers did not address their children's environmental exposures. In another study, Georgia pediatricians acknowledged that environmental history taking would help parents protect their children from hazardous environmental exposures, but few reported having had any training in it, and most rated their self-efficacy related to this task as poor (16). In three other studies, Connecticut physicians, Canadian family practitioners and Australian general practitioners, rated their knowledge low in most environmental health issues (17, 18) or believed they had inadequate access to environmental health information (19).

AAP members also expressed an inability to respond to questions about anthrax and nuclear attacks. Published data on bioterrorism reveals a parallel lack of training: 79% of American Medical Association (20) and 74% of American Academy of Family Physicians members (21) feel unprepared to respond to such an event. Additionally, Northeastern nurses, doctors, hospital security officers, medical students and nursing students answered less than one-fourth of knowledge questions correctly in a test of chemical and biological terrorism facts and policies; less than 23% felt confident in rendering care (22).

Study Limitations

The combined response rate of 36% is a limitation to this study. While electronic submission enabled faster data collection, its usage may have also compromised cooperation; our calculations show that the reply rate via e-mail was lower than that achieved via postal mail. Higher success rates might be attained by proofreading e-mail addresses within the database, verifying that these addresses are still active, and ensuring that list-serve e-mails are not filtered directly into junk-mailboxes. Future attempts at web-based physician surveys must also consider the proportion of the target audience that has Internet access; only 50.6% of AAP members provided e-mail addresses. The analysis of nonresponders and concomitant biases was discussed previously (14).

Conclusion

With 1,396 responses included in our study, we have, to our knowledge, conducted the largest survey of physicians, and certainly pediatricians, about environmental health and terrorism concerns to date. Additionally, by targeting the tri-state area, we sampled practitioners who were most likely to see children directly affected by the environmental health and bio-terrorism consequences of the World Trade Center attacks.

Strikingly, among the variables measuring adequacy of information about the health effects of the WTCD and knowledge of environmental health issues, there was very little variation among subpopulations. Such a finding implies that all practitioners, nearly regardless of race/ethnicity, age, practice location, specialty, years in practice, and practice setting, would benefit from education. The survey suggests a special need among those caring for children presenting with environmental health and bioterrorism-related complaints and/or concerns. Efforts may be targeted towards these individuals, since the association between this need and geographical location, gender, race and specialty may allow them to be readily identified. The analysis of responses by practice setting and specialty suggests a role for pediatric associations. Those who work in hospitals may receive information from their institutions, but other initiatives, led by physician groups, could supplement this knowledge as well as reach those in private practice. The content of medical education must be updated for faculty and trainees alike; the involvement of the Association of Pediatric Program Directors and the Ambulatory Pediatric Association may be crucial in overcoming the disparities observed between residents and other physicians and in preparing them to respond competently to the practice demands that they are already experiencing.

Since the WTCD, some information has been available to child health professionals. The AAP Committees on Environmental Health and Infectious Diseases published a broad review of various chemical-biological agents in 2000 that highlighted the lack of guidelines for the treatment of children: for most of the accepted vaccines and antidotes, neither efficacy nor side effects have been confirmed, and appropriate dosages have not yet been established (12). In 2002, the AAP released a policy statement on smallpox vaccination with limited information on recognition of the disease, calling again for further research on the safety and immunogenicity of the vaccine in children (23). An AAP policy statement on radiation disasters was issued after the closure of our survey, in 2003, providing descriptions of the early and late effects of exposure, as well as recommendations for decontamination and the use of potassium iodide (24). In the same year, the AAP published a second edition of its Pediatric Environmental Health handbook. Its chapters on outdoor air pollutants and chemical-biological terrorism do describe the characteristics of those exposures, but more detailed instructional information for practitioners may be needed (13, 25).

More recently, other groups (26, 27) have provided more specific, comprehensive and practical information. Professional organizations representing physicians who care for children may be well positioned to distribute guidelines and relevant information based upon the most current and evidence-based recommendations. And their efforts could be aided by the effective dissemination of materials, and evaluated with repeated measurements of caregivers' knowledge and skills. A major challenge of targeting nuclear events and bioterrorism for educational purposes is their relative rarity of occurrence. Child health professionals should be provided with the means of accessing current information relative to effective responses during and after an event, and sufficient base knowledge before these acute situations. Preparedness education and protocol development may be of paramount importance. To be successful, these educational efforts must be made in collaboration and coordination with strong public health responses.

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Resident as Teacher:

Educating the Educators

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Abstract

Background: Medical students receive their clinical training from various sources: from residents during informal teaching sessions and from attending physicians during more formalized rounds. As a result of the increasing pressures of clinical medicine, efforts need to be focused on the identification and training of the next generation of clinical educators.

Description: We have created a pilot medical education elective for residents which pairs training in teaching skills with formal teaching opportunities during protected blocks of elective time, an opportunity which is rare in most residency programs and may provide for more effective teaching skill acquisition.

Results: Feedback from the participants demonstrates widespread acceptance of the pilot program.

Conclusions: We believe this new model would provide motivated residents with the skills and the protected time to teach, and help create a future generation of attendings better able to teach.

Key Words: Medical education, resident-as-teacher programs, teacher training.

Introduction

The Millennium Conference on the Clinical Education of Medical Students (2001) convened representatives from top United States medical schools to define the state of clinical medical education (1). One aim of this conference was to identify the individuals who provide clinical training for medical students. The group acknowledged that medical students receive their clinical education from a diverse group of individuals, including nurses, residents and attending physicians, and allied health professionals. Residents teach students informally, by asking questions, giving mini-lectures, demonstrating procedures and physical examination skills, and teaching day-to-day management related to specific patients. Attending physicians, on the other hand, often have scheduled time with students as assigned preceptors or teaching attendings. Unfortunately, due to the time demands and economic pressures of contemporary medical practice, attending faculty are becoming more difficult to find. Nutter and Whitcomb note that faculty time is limited by increasing economic pressures, administrative responsibilities, and other competing endeavors (2). They claim that this is especially true for voluntary faculty and that many schools report increasing difficulty recruiting attending faculty from the institution, especially since fewer than half of the medical schools pay their clinical preceptors to teach.

With fewer attending faculty available to teach, medical schools must either find new teachers or broaden the existing roles of other educators. Some schools have already recognized this and have begun to utilize senior medical students as clinical teachers (3). We suggest that house officers would also function well in more formal teaching settings if given the opportunity. In fact, according to one study, medical students report that one-third of their knowledge already comes from residents' teaching (4).

Despite the fact that residents play a critical role in undergraduate medical education, clinical responsibilities often limit their opportunities to teach. Due to the increasing pressure of caring for more and sicker patients while still learning clinical material, managing a team, and abiding by state and national work-hour restrictions, residents must often assign teaching a lower priority. When Apter

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and colleagues wrote about the important role of the resident as teacher, they acknowledged that resident teaching could be enhanced if residents were freed from some of their service obligations (5). An investigation of internal medicine residents' teaching experiences at New York University also revealed a tension between clinical work and teaching; as one resident stated, "If we [the team] get all the work done, then I'll teach" (6). Although time conflict in medicine is a complex barrier that can never be removed and one that clinicians must learn to manage, the pressures of residency are at a maximum and may hinder residents' abilities to learn the skills of teaching.

The purpose of this article is to describe the process we are using to expand the role of the resident-as-teacher at our institution. We first review principles of adult learning and illustrate how these principles apply to clinical medical education and the role of the resident as teacher. We then examine programs designed to enhance resident teaching. Finally, we describe a pilot medical education elective for residents which pairs training in teaching skills with formal teaching opportunities during protected blocks of elective time.

Residents Should Teach: Adult Learning Theory

Educational theory recognizes today's medical students as adult learners. Much of our current understanding of adult learners and adult learning theory comes from the work of Malcolm Knowles. Knowles used the term "andragogy," which he defined as the art and science of helping adults learn (7). His work is based on the assumption that adult learners seek information with immediate applicability and value learning that speaks to challenges of daily life. In the clinical setting, residents are experts in determining what is practical and relevant. They can teach students the medical knowledge and skills needed to be a good clinical clerk and house officer, including presentation and note-writing skills, the mechanics of ordering tests, and many other topics less formalized, but equally important, for being a physician (8).

Adult learning theory also proposes that adult learners thrive in a supportive learning environment. The temporal proximity of residents to their medical school experience and their intermediate position in the hierarchy of medical education, may prove beneficial in helping to create a comfortable learning environment for their students (8). According to Knowles, adults also prefer to be self-directed in their learning, which would explain why residents, themselves adult learners, desire teaching tools to make themselves more efficient in teaching other members of their team and their patients. Knowles' theories, in fact, encouraged us to move forward and design our resident teaching elective.

Residents Can Teach: Resident-as-Teacher Programs

Residents can be effective teachers, but they also benefit from formal training. Several studies have established the role of the resident as teacher and the need to better train residents to teach (9–11). Greenberg was among the first to write about the role of residents as teachers; he asserts that "knowledge…should not be confused with proficient teaching skills" and that most residents who have sufficient knowledge still feel inadequate as teachers (11). Irby writes that "to be an effective [clinical] teacher, one must also have experience with patients and recall them at appropriate times, be able to deduce the educational level of the learners, know general principles of teaching and learning, and have lessons to teach about topics" (12). Essentially, medical knowledge is only one component of being an effective clinical teacher.

Many benefits of resident teaching programs have been suggested in the literature. Among these are the enhancement of the resident's knowledge base, communication skills, and self-directed learning skills. It has also been suggested that these programs can prepare residents to be more effective mentors to medical students and colleagues, and increase the pool of interested faculty preceptors for the future (13, 14).

A 2001 survey by Morrison et al. estimated that only 55% of residency programs offered formal training in teaching skills (15). This training was most prevalent in internal medicine, pediatrics, and combined internal medicine-pediatric residency training programs. Encouragement to provide teaching skills programs for residents has come from both the Liaison Committee for Medical Education (LCME) and the Accreditation Council for Graduate Medical Education (ACGME). The LCME states that house officers must be prepared for their role as educators and evaluators of medical students (16). The ACGME, in their outcome project, requires residency programs to assure competence in the area of teaching (17). Resident-as-teacher programs have been utilized to address these mandates.

What are the ultimate benefits of these teach programs: Specifically, training residents to teach facilitates effective information exchange among the medical team, residents, patients, and families (in ACGME language, effective patient care and interpersonal communication skills) and also facilitates the learning of students and other health care professionals (practice-based learning and improvement).

Literature from institutions that offer resident teaching workshops indicates that teaching skills can be taught (4, 10, 18–20). In one study, residents were surveyed two years after a teacher-training program; 61% of residents were using techniques and principles from the course in their teaching and 67% were able to recall and explain some of these principles (20). Furney et al. studied the effectiveness of the Neher Microskills Model (a teaching technique used to help clinicians with limited time to teach) among resident teachers and documented statistically significant improvements in the residents' ability to involve the learner in decision-making, evaluate the knowledge of the learner, offer suggestions for improvement, provide feedback, and motivate the learner to read (19). Another study suggests that teaching residents to teach can improve both their medical knowledge and communication skills; in this study, residents assigned to teach reported increases in their own knowledge of the subject (21). A recent literature review of resident-as-teacher workshops confirmed that resident teaching courses improve residents' self-assessed teaching behaviors and confidence as well as student evaluations of resident participants (22).

Few studies address the wider impact of resident-as-teacher programs, specifically the possibility that imparting teaching skills to residents can also enhance their clinical skills. Sheets et al. found that residents believe that teaching students increases their own clinical and intellectual skills (23). This was supported by Busari and Scherpbier, whose study affirmed that teaching medical students helped residents to become better clinicians, since "teaching stimulates critical thinking and reflection on knowledge" (14). In his paper, Schiffman asserts that house officers who teach benefit themselves, their students and their patients, because of the enhanced communication skills that come as a result of knowledge of teaching principles (24). Others have noted that residents who teach enhance their own growth and development as clinicians, since teaching helps them to "organize, systematize, and rehearse" knowledge and skills as well as "promote better patient care and patient education because teaching the patient is often a critical aspect of being an effective doctor" (25).

Although much of the data on the successes of resident-as-teacher programs are based on self-reports and student assessments, more rigorous trials are now demonstrating measurable results. For example, Morrison et al. showed that primary care residents improved in several domains of teaching on an Objective Structured Teaching Examination taken after a resident-as-teacher course (18).

Residents Teaching: Development of a Teaching Elective

Teaching workshops alone are of little value if the participants are not given opportunities to practice their learned skills. Since adult learning theory states that learning is best accomplished when information is immediately applicable, the juxtaposition of a teaching course with protected time to practice these new skills seems appropriate.

In 2001 the Institute for Medical Education at the Mount Sinai Hospital created a successful teaching program for residents (26), to improve the teaching and leadership skills of residents at Mount Sinai and all clinical affiliate institutions. The program, based on adult learning theory, involves a seven-hour curriculum delivered to post-graduate year 2 (PGY-2) residents separately in the departments of Internal Medicine, Pediatrics, Obstetrics and Gynecology, Psychiatry and Surgery. The course reviews practical teaching techniques, setting goals and expectations, basic teaching theory, and feedback.

We also created an elective that offers residents who have participated in the formal Resident Teaching Development Program (RTDP) the opportunity to learn more about educational theory and to practice teaching while freed of the constraints of a ward team leader. We piloted this program with a chief resident (MW) in the Internal Medicine-Pediatrics program at the Mount Sinai Hospital. The resident first reviewed principles of adult learning with a faculty mentor (JK) as a way of reviewing teaching techniques, and developed goals for his teaching sessions. Potential teaching opportunities in the departments of Medicine and Pediatrics were then identified. The teaching opportunity selected by this resident was that of clinical preceptor for third year medical students during their pediatric clerkship. (The clinical preceptor reviews student case presentations, both written and oral, and teaches physical diagnosis at the bedside.) The resident met bi-weekly with his faculty mentor to discuss assigned readings on adult learning theory and small group facilitation. Teaching sessions with students were supervised by an experienced teacher who provided feedback to the resident after each session. Medical students and a faculty member also formally evaluated the resident at the end of the elective.

For the resident, this experience proved useful as a way of reinforcing the teaching skills initially taught during Mount Sinai's second-year resident-as-teacher program (RTDP). It also allowed the resident to shift to a more "attending-like" mindset, focusing on the most crucial teaching points and the most interesting aspects of a case, rather than the minutiae involved in managing an acutely ill patient. Discussions were lively, broad ranging, and low key. Unlike teaching on the wards, where time is a constant pressure, preceptorial meetings can focus on the presentation of one patient for as much as 60–90 minutes, and allow ample time for the resident to provide feedback on the student's presentation and history-taking style. This setting also provides a safe environment for bedside teaching. Challenges for the teaching resident are similar to those challenges that face any teacher who facilitates small groups, and include teaching to various levels of learners, poor group dynamics, and lack of participation.

Student evaluations of the experience were positive. In their feedback, students wrote that the teaching resident was a strong teacher and role model. One noted that the resident "showed…just how big…of a role a [third year student] can have on a team…[The teaching resident] was a model for the type of resident I want to be." Another student described the teaching resident as a strong teacher who was "very thorough and detailed." His faculty mentor described the resident as an "outstanding preceptor," to whom the students "eagerly responded."

Discussion

Many individuals play crucial roles in the clinical training of medical students. However, the traditional method of ward-based medical education is no longer adequate, given the diminishing number of available faculty preceptors and the inability of residents to take full advantage of teaching opportunities. Training residents as teachers can enhance residents' self-perceived medical knowledge, their communication skills, and perhaps even their abilities as clinicians. Providing interested residents with protected time to teach medical students in a formal setting (perhaps as part of a teaching elective) has benefits for both the student and the resident. Students learn well in a safe, self-directed environment where they are free to ask questions and find their own answers. Residents benefit by learning practical and widely applicable teaching skills, improving their grasp of the material, and, perhaps, enjoying the responsibility and the teaching process. We hope that providing residents with a unique opportunity to study teaching skills and apply them immediately in a realistic yet supportive environment will help create a cadre of excellent clinician-educators in the future.

Despite the recognized increase in self-assessed teaching skills, there is little objective data on clinical outcomes of resident-as-teacher programs. One frequently asked question is whether training residents to teach produces better clinicians. This query has not been answered yet (except by self-report) because clinical outcomes are difficult to assess and many believe that producing better teachers and better-educated medical students may be a sufficient end. Still, the question of whether better teaching skills lead to better doctor-patient communication and better overall patient care warrants consideration.

Some residents at Mount Sinai already teach in addition to their usual inpatient duties: they teach physical diagnosis during the first and second year and they mentor small groups during the clinical skills orientation course and spring intersession period for third year students. Our elective, however, creates a more formalized teaching and learning experience for interested residents, one in which where they have time to focus on clinical teaching, practice teaching skills, and receive feedback and guidance from an expert clinical educator. We hope to match teaching experiences with interests and abilities for all our residents, perhaps in the context of a resident educator track.

Our new elective requires that we investigate the effects on the medical student of having a resident preceptor. Specifically, do students prefer the experience of having resident preceptors and are students learning at least as well with residents as they would with faculty preceptors? Clearly, residents can and should teach. Creating a teaching elective for them will probably improve the medical students' education, increase the teaching ability of the residents, and provide a forum to begin the research that will assess the effects of this new intervention.

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Letter to the Editor

Sepsis-Induced Disseminated Intravascular Coagulation:

A Rare Complication of Sacrococcygeal Pilonidal Sinus Disease

THE TERM "SACROCOCCYGEAL PILONIDAL SINUS" describes one or more midline openings in the natal cleft. It was first reported by Mayo in 1833, and although in the 1950s pilonidal sinus disease (PSD) was thought to be of congenital origin, it is now widely accepted to be an acquired disorder. PSD is a common hair-containing sinus or abscess, and initially 50% of patients present with a pilonidal abscess. During the last century physicians focused their efforts on etiology and medical management of PSD (1–3).

A 22-year-old white male, a beach cleaner by profession, was admitted to the emergency unit of the Clinical Hospital of Split because of fever and coma. In the previous few weeks he had occasionally complained of headache, but his medical history, elicited from the patient's mother, did not reveal a history of illness or drug abuse, or a family predisposition to any disease. The day before admission his body temperature was 37.3°C and he complained of headache and dizziness. On admission, he was perspiring profusely, his pulse rate was 144/min, blood pressure was 100/70 mm Hg, respiratory rate was 27/min, and body temperature was 41.5°C. He was in a coma, with a Glasgow Coma Scale (GCS) score of 3. His body mass index was 32.

Upon admission, he vomited coffee-ground-colored matter (hematemesis), so nasogastric tube lavage was performed to clear the stomach of clots and fresh blood. Endoscopy revealed erosions of the middle and lower parts of the esophagus and duodenal postbulbar segment. Nasogastric suction content sent for chemical-toxicology analysis was negative. The patient's laboratory parameters indicated sepsis with disseminated intravascular coagulation: prothrombin time 41% (normal range 75–100), INR 1.65 (0.9–1.08), activated partial thromboplastin time 45 s (21–32), platelet count 33 × 10^9/L (140–440), bands 26% (0–5), fibrinogen 4.07 g/L (2–4.1), D-dimer 1,535 μg/mL (<250), factor V 25% (60–140), factor VII 30% (60–140), factor VIII 48% (50–200), factor X 58% (60–140), factor XII 44% (60–140), antithrombin III 70% (80–130), and C-reactive protein 188 (0–3).

Urine sent for qualitative drug abuse screening (benzodiazepines, opiates, methadone, amphetamines, cocaine, barbiturates, phencyclidine and cannabinoids) and a test for alcohol in the blood were negative. Blood samples for microbiological analysis were taken. Urine and chest X-ray didn't reveal any pathological findings. Spinal fluid sent for microbiological analysis was negative. Physical examination revealed inflamed sacrococcygeal pilonidal sinus (erythema and swelling over the sacrococcygeal region), but physicians didn't consider the PSD to be a cause of sepsis.

The patient was intubated and a Foley-urine catheter was placed. Computed tomography of the brain revealed massive edema, especially in the mesencephalon, with a smaller amount of subarachnoidal and marginal petechial hemorrhage. The patient was sent to the intensive care unit, where mechanical ventilation (IPPV), TV=750 mL, f=12, FiO2=0.40), crystalloid and colloid solutions, dexamethasone 4 × 1 amp i.v., analgesic sedation medications (fentanyl, midazolam), and 6 U of packed platelets were administered. Antibiotics (cefepim 3 × 2 g i.v., gentamicin 240 mg i.v., and metronidazole 3 × 500 mg i.v). were given.

On the second day, an inflamed pilonidal sinus (6 × 4 cm) of the sacrococcygeal area became more apparent. Before the surgical procedure, purulent sinus samples were sent for microbiological analysis. Radical excision of the pilonidal sinus down to the presacral fascia was done, without primary closure of the wound. Laboratory examination showed pathological values: AST = 1920 IU/L (1–38), ALT = 2133 IU/L (1–41), urea 10 mmol/L (2.5–8.3), creatinine 231 mmol/L (54–116), lactate dehydrogenase = 2,833 IU/L, and still low platelets = 31 × 10^9/L, so 6 U of packed platelets and low-molecular-weight heparin (enoxaparine, Clexane, Aventis Pharma, 0.8 mL/80 mg bid s.c.) were administered. HIV and hepatitis B and C viral infection were excluded.

Bacteroides fragilis was isolated from hemoculture and sinus fluid samples, so amoxicillin and clavulanic acid (3 × 1.2 mg i.v.) and clindamycin 3 × 600 mg i.v. were introduced. Brain CT showed reduced edema, without sign of intra- or extracerebral hemorrhage.

After 7 days in the intensive care unit, the patient was hemodynamically stabile, in good condition, with laboratory values within the normal range. Microbiological analysis of blood samples and purulent material from the sinus identified the same pathogenic bacteria, *B. fragilis*, so we concluded that acute inflamed pilonidal sinus was the cause of sepsis. Bioptic material showed encapsulated nests of hair with purulent infection. The wound healed, without any sign of inflammation spreading to the surrounding area. Histological analysis revealed foreign body granuloma. After 10 days the patient was released and there were no long-term sequelae.

Although pilonidal disease has been known since 1833, only a few published reports about life-threatening complications of PSD have appeared. Verdu et al. described the rare case of a male diabetic patient with a recurring pilonidal cyst, who developed a lumbar osteomyelitis and epidural abscess three weeks after pilonidal cyst excision with epidural anesthesia, with a fatal outcome despite emergency treatment (4). Borer et al. described septic arthritis due to *B. fragilis* after pilonidal sinus resection, in a patient with rheumatoid arthritis (5). Velitchkov et al. published the rare case of a previously healthy adult male who developed necrotizing fasciitis and toxic shock syndrome, both of which complicated neglected sacrococcygeal PSD associated with *Streptococcus pyogenes* and *B. fragilis* (6). Shlasko et al. described a case of toxic shock syndrome due to staphylococcal infection occurring in a previously healthy young man after elective surgery for a pilonidal cyst (7). In 1982 Friis and Madsen described recurrent toxic shock syndrome in a man, after surgery for a pilonidal cyst, and Cobb et al. published a case report of toxic-shock syndrome in a young man with a pilonidal abscess (8, 9).

Risk factors for PSD are white race, male sex, family predisposition, increased sweating, activity associated with sitting and buttock friction, sedentary lifestyle, poor personal hygiene, obesity, and local trauma. The incidence rate of pilonidal disease is approximately 0.7%, the disease occurs 2.2–4 times more often in men than women, and the average age of patients at presentation is 21 years (1, 2). PSD involves a combination of skin and perineal flora. *Staphylococcus aureus* is the most common organism and *B. fragilis* is the most common anaerobe. Although numerous randomized clinical studies have evaluated different treatments, no clear consensus has been reached as to the optimal medical or surgical treatment (10).

Until now there have been only four published case reports about toxic shock syndrome in male patients with PSD, usually after surgical treatment, and associated with *Staphylococcus, Streptococcus* and *B. fragilis* infections. We have presented a case of disseminated intravascular coagulopathy (multiple organ failure: liver and renal failure, and massive brain edema with subarachnoidal and marginal petechial hemorrhage, and erosions of esophagus and duodenum) in a patient with severe sepsis due to neglected pilonidal abscess, which successfully responded to antibiotics, and symptomatic and surgical treatment. *B. fragilis* was isolated from his hemoculture and sinus fluid samples.

Previously published case reports of unusual complications of this illness have also concerned males (4–9), perhaps because the incidence of PSD is higher among males. The case is remarkable for its favorable and quick outcome and its rarity.

The case serves as a reminder that neglected pilonidal abscess can lead to unusual and life-threatening consequences, even in a previously healthy patient. When a patient presents with sepsis of unknown source, physicians should consider PSD as a possible cause.

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